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British Journal of Anaesthesia

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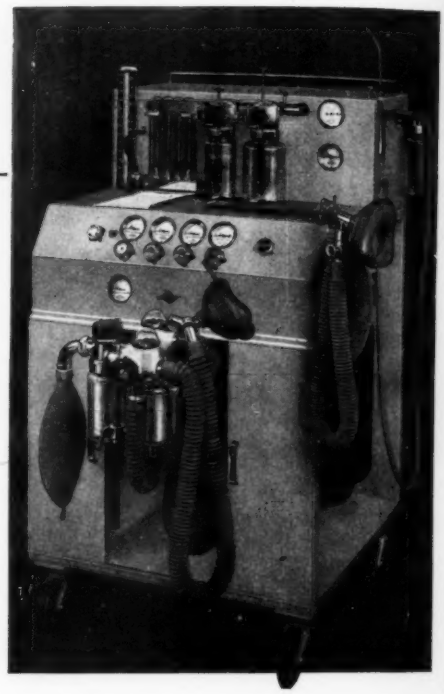

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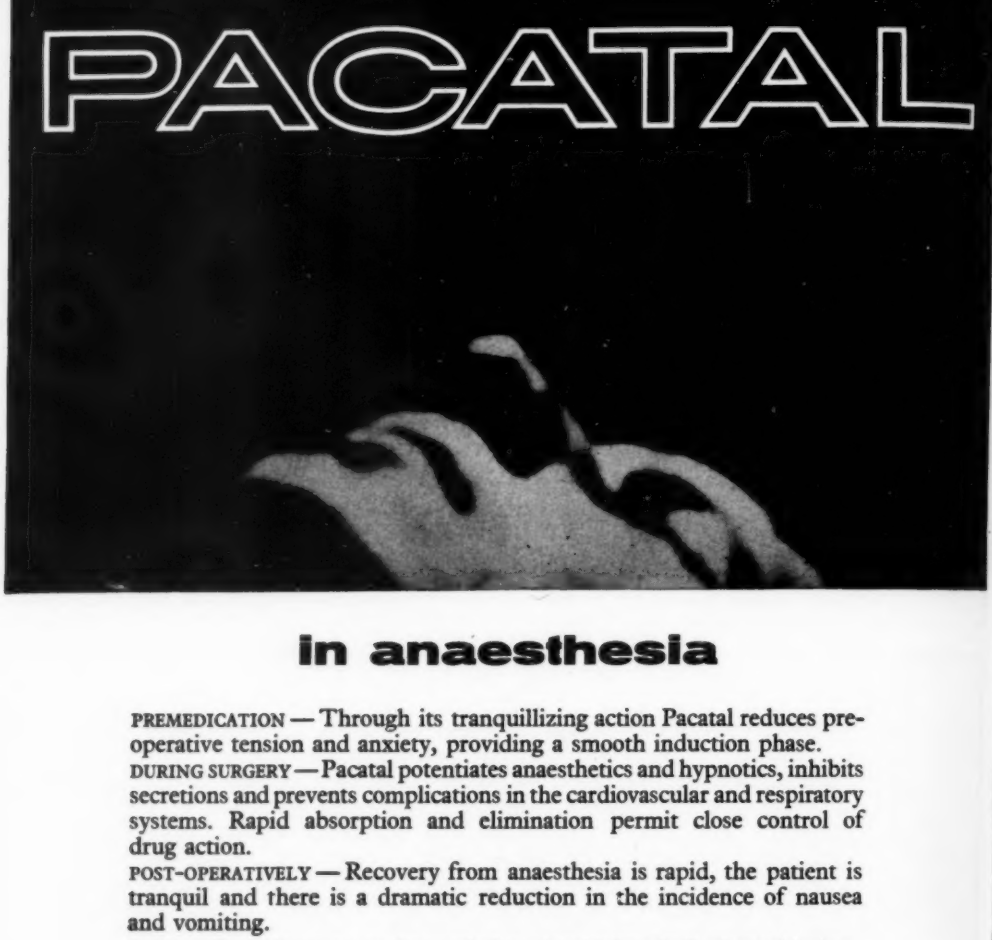

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VOL. XXIX, No. 6 JUNE 1957

EDITORIAL

" It is the truth alone that we desire to know, and
what joy does it not give to have sought it out."
Carl Wilhelm Scheele (1742–86)

PROFESSOR BEECHER'S account, in this issue of the Journal, of the work of his team, now twenty-one years old, should give ample food for thought to those of our readers who have the urge to do research. The growing facilities in this country have led to an ever accumulating source of knowledge. In view of the difficulties of carrying out research, it is not surprising that all the published papers do not show a high standard of work. It may be wise, therefore, to consider ways in which this might be improved.

Clinical research workers are liable to get caught up with the dictates of opportunity, and often tend to embark upon courses of research without much forethought. Since there are many inviting opportunities, the temptation to divide one's energies is of no mean order, but if more than one subject is selected for study, they must be carefully chosen. Pursuit of unrelated research projects may lead to a superficial knowledge, and to temporary holdups; whereas, if several related projects are undertaken, a deeper understanding should result.

A combined attack on any problem by experienced men is likely to be far more productive than that of a single worker. Team work is not adequately covered by the provision of a unit composed of different specialists. The director must have selective ability and be capable of finding individuals who are willing to co-operate and yet remain critical. One important aim is to keep the team working for a number of years. Because they have fundamental contributions to make in our subject, basic scientists should be drawn into close association with clinicians, and since each may have equal value as members of the team, the financial arrangements should not be as disproportionate as they are at present. The work of basic scientists may lead them away from the clinical sphere, and there should be enough of them in a team to allow for the expansion of their ideas.

The passage of a further decade will show the impact of our researches, and it remains to be seen how far they will affect the practice of anaesthesia. Much will depend on how well we have planned at the beginning.

Brit. J. Anaesth. (1957), **29**, 242

THE PHYSIOLOGICAL ACTION OF NEUROMUSCULAR AND GANGLIONIC BLOCKING AGENTS

BY

J. H. BURN

From the Department of Pharmacology, University of Oxford

The neuromuscular junction. Our knowledge of the physiology of the neuromuscular junction has been advanced greatly within the last ten years, and a consideration of the action of neuromuscular blocking agents must be introduced by a summary of what we have learnt. The contraction of a muscle cell occurs when an electrical charge which exists on the membrane surrounding the cell is removed; the cell membrane is then said to be " depolarized ", and contraction is the result. Nothing is known of the process whereby the removal of the charge causes contraction, and discussion must be confined to the events leading to depolarization. The best account of these events is that given by Hodgkin (1951).

Activity of the cell membrane in resting muscle. The term " membrane " for the outer wall of the cell is misleading, as it suggests a thin lifeless barrier. In fact, the cell membrane is a highly complex structure in which metabolic processes occur. These processes provide energy which is used to drive sodium ions out of the cell, and the mechanism which removes the sodium ions has been called the sodium pump. As a result of this mechanism the concentration of sodium ions within the cell is less than that outside; thus in the frog sartorius muscle the concentration in the cell is about one-seventh of that in the plasma. While the concentration of sodium ions is less than that outside, the reverse is true for potassium ions, and the difference is greater. In frog sartorius the concentration is about 50 times higher inside than outside. The processes in the cell membrane thus not only drive sodium ions out of the cell, but drive potassium ions into the cell, and in some tissues these two processes appear to be connected. Potassium ions can only be pumped in when sodium ions are being pumped out.

The electrical charge on the cell membrane arises because of these differences in ionic concentration between the inside and the outside of the cell. The charge is positive on the outside of the membrane and negative on the inside. The size of the charge is closely related to the difference in potassium concentration between inside and outside, and when the charge is measured by inserting an electrode inside the cell, the " membrane potential " so obtained is found to vary in linear relation to the external potassium concentration, the membrane potential being high when the external potassium concentration is low. When the external concentration of potassium is raised until it is equal to the concentration inside, then the " membrane potential " falls to zero, that is to say, the charge on the membrane vanishes and the membrane is depolarized; as a result the muscle contracts.

Changes occurring during contraction. At rest the membrane of the muscle cell is an effective barrier to the entry of sodium ions, and it remains a barrier until the charge which it carries is neutralized. As the charge is positive outside the membrane, it can be neutralized by applying a cathode which is negative. The muscle then contracts. If the electrical changes which precede a contraction are recorded by an electrode inside the muscle cell, there is a fall from the negative potential of 90 mV not only to zero but to a positive potential of 40 mV. This fall is due to the entry of sodium ions into the cell, because the membrane has become permeable to sodium ions. After this change the permeability of the membrane to sodium diminishes and that to potassium increases. Potassium flows out of the cell, and in doing so re-establishes the charge on the membrane, and the potential becomes once more a

negative potential of 90 mV. The change in the membrane potential which precedes contraction is therefore in the main a transient depolarization, but it is called an action potential. It would have been more logical to call it an action depolarization.

The action of acetylcholine. The transmission of a nervous impulse to skeletal muscle is due to the liberation of acetylcholine, and this substance acts as a depolarizing agent (Katz, 1956).

Its action is exerted at special points in the muscle where the nerves terminate. At these points there are microscopic structures known as motor end plates, which are highly sensitive to acetylcholine. The muscle fibres themselves are far less sensitive to acetylcholine, and normally are not excited by it.

The motor end plate is a highly differentiated part of the muscle membrane having a large area due to the surface being folded. When a nerve impulse arrives at a motor end plate it causes a local depolarization which is called an end plate potential.

If this end plate depolarization is sufficient to cause the potential to fall from 90 mV to about 50 mV, then the electrophysiologists say " at this point the membrane potential becomes unstable and the potential change continues automatically, giving rise to a brief spike of 130 mV amplitude " (from 90 mV negative to 40 mV positive). Or, in other words, when the charge on the membrane has become reduced from 90 mV to 50 mV, the permeability to the sodium ions is now so much increased that they pour through the membrane until the potential has been completely reversed.

This spike is propagated as an excitation wave towards the ends of the muscle fibre. For when the part of the muscle under the motor end plate is depolarized, it acts as a short circuit for the charge on adjacent parts of the muscle membrane, and these parts in turn become depolarized; in this way the " action potential " travels to the ends of the muscle fibre.

The release of acetylcholine. The motor end plate is thus a mechanism which can be activated by acetylcholine and which is therefore believed to have receptors with which the molecules of acetylcholine combine. Electrical recording of the changes which occur in the end plate has shown that it is bombarded by minute quantities of acetylcholine which are released spontaneously from the nerve endings even in the absence of a nerve impulse (Fatt and Katz, 1952). These tiny amounts of acetylcholine cause small local depolarizations (small " end plate potentials "). The acetylcholine is released in packets containing probably some thousands of acetylcholine molecules, the packets all being of about the same size. That a chemical transmitter substance should be continually released in this way is extremely interesting. Small submicroscopic vesicles of a mean diameter of about 200–300 Å have been observed inside the motor nerve terminals and these may be the containers of the quantum of acetylcholine.

When an impulse comes along the motor nerve a large number of packets of acetylcholine is suddenly released. Their effect in producing the end plate depolarization (end plate potential) is different from that of an electrical stimulus applied directly to a muscle fibre as described above. For the change in potential is smaller, and seems to be explained by the suggestion that acetylcholine causes, not an increase in permeability for sodium ions only, but a general increase in ionic permeability which applies to potassium ions as well, so that sodium ions enter and potassium ions leave the motor end plate simultaneously. When the end plate potential is sufficiently large, that is to say, when the depolarization has reduced the membrane potential sufficiently far, it gives rise to an abrupt spike of much greater depolarization. Thus acetylcholine short-circuits the surrounding muscle membrane, providing a pathway whereby the external and internal charges on the surrounding muscle membrane can neutralize one another. Thus the muscle membrane is depolarized, and as a consequence contraction occurs.

NEUROMUSCULAR BLOCKING AGENTS

The action of d-tubocurarine. Relaxing agents are of two kinds, the first kind being represented by d-tubocurarine and gallamine, the second kind being represented by decamethonium and suxamethonium. The first kind are said to be competitive inhibitors of acetylcholine.

When d-tubocurarine is injected intravenously into an animal or when it is applied to a nerve-muscle preparation in a bath it exerts no contractile effect; it does not stimulate the muscle. However, in the presence of sufficient d-tubocurarine the nerve impulse is ineffective in making the muscle contract. When the electrical changes in the endplate region are examined it is found that in the presence of, first, small, and then of increasing amounts of d-tubocurarine, the end plate depolarization is gradually diminished until it is no longer sufficient to give rise to the sudden spike of much greater depolarization which is responsible for the muscle contraction. These observations are interpreted by saying that d-tubocurarine combines with some of the receptors with which acetylcholine combines when it is about to depolarize the end plate. If many or most of the receptors are engaged by molecules of d-tubocurarine, then there are few or none with which acetylcholine can combine, and the depolarization of the end plate is much less than before, or it does not occur at all. If there is no depolarization of the endplate, there is no contraction.

The combination between d-tubocurarine and the receptors thus inhibits the action of acetylcholine, but the inhibition is competitive. That is to say, the extent of the inhibition depends on the relative proportions of d-tubocurarine and acetylcholine present. If the concentration of acetylcholine rises, some of the molecules of d-tubocurarine will be removed from their combination with receptors, and these will be free to combine with acetylcholine. The end plate depolarization will therefore be greater. The concentration of acetylcholine at the nerve ending can be raised by neostigmine; this substance combines with the cholinesterase which destroys acetylcholine, and as a result the concentration of acetylcholine reaching the end plate receptors after a nerve impulse is much greater, because fewer of the molecules are destroyed.

The action of decamethonium and suxamethonium. The other group of relaxing agents which includes decamethonium and suxamethonium differs from the first group because it comprises agents which resemble acetylcholine in causing depolarization of the motor end plate. Thus when these compounds first reach the motor end plate they cause muscular contraction which is ordinarily seen as fasciculation of the muscle. In a cat, however, if decamethonium is injected into an artery close to its entry into a muscle, it causes a powerful twitch. After the injection there is neuromuscular block and the muscle is relaxed. This block has been thought by some to be due to the persistence of the depolarization caused by decamethonium. The block has been believed to result from failure of the process of repolarization and attributed to the stability of decamethonium which is not destroyed by cholinesterase. The evidence indicates that this explanation is incorrect and that the neuromuscular block is due to another cause. Not only does decamethonium depolarize the motor end plate, but in addition its action extends to the muscle fibres themselves on each side of the motor end plate, and it renders these muscle fibres inexcitable (Burns and Paton, 1951). It is to the great reduction in the excitability of the muscle fibres near the end plate that the neuromuscular block caused by decamethonium and suxamethonium appears to be due. The neuromuscular block develops during depolarization but it persists after repolarization is complete.

If we imagine a group of long muscle fibres with a nerve approaching the group at right angles and ending on a motor end plate situated in the middle of their length, then when the neuromuscular junction is blocked by d-tubocurarine, a stimulus applied directly to one end of the fibres travels to the other end unaffected by the neuromuscular block. If, however, the neuromuscular junction is blocked by decamethonium Burns and Paton (1951) showed that a stimulus applied directly to one end of the fibres is unable to pass through the muscle in the neighbourhood of the motor end plate, because the muscle in that region is inexcitable.

There are other differences between the action of d-tubocurarine and of decamethonium which may be described. When these two substances are compared in different species, or in different muscles of the same species, animals or muscles which are sensitive to d-tubocurarine are relatively insensitive to decamethonium, and vice versa.

Another difference is that block with decamethonium is not diminished by neostigmine, as is block with d-tubocurarine. A third difference is in the reaction of patients with myasthenia gravis. These patients are extremely sensitive to the action of d-tubocurarine, but unusually resistant to the action of decamethonium.

While the difference in the action of d-tubocurarine, on the one hand, and of decamethonium on the other hand is clear, it must be said that the foregoing account is probably incomplete, and that more remains to be discovered. The evidence described suggests that the two kinds of neuromuscular block have nothing in common and are unrelated. This, however, is not true. There is an inverse relation. As already stated muscles which are sensitive to d-tubocurarine are insensitive to decamethonium, and vice versa. Further it has been shown that decamethonium and suxamethonium produce neuromuscular block in the monkey and the dog which begins with depolarization, but later in the same experiment resembles that produced by d-tubocurarine (Zaimis, 1951). The conclusion seems inevitable that there is a closer relation between the two kinds of block than is yet understood.

The action of suxamethonium. The use of suxamethonium as a relaxant has now become widespread because its duration of action is normally short. Suxamethonium is destroyed by cholinesterase in the same manner as acetylcholine.

There is, however, a proportion of patients in whom neuromuscular block persists for longer periods and this event, for which the anaesthetist is not prepared, gives rise to alarm. The cause of the protracted relaxation is not yet clear. The commonest explanation which is given is that a patient in whom this prolonged action is seen is one who is deficient in pseudocholinesterase, this being one of the enzymes which split choline esters such as acetylcholine and suxamethonium. Wide variations in the amount of pseudocholinesterase are known to occur.

A second explanation is to be found in the observations made by Grob, Johns and Harvey (1955). These workers applied supramaximal stimuli to the ulnar nerve of normal human subjects, and placed electrodes on the skin over the abductor muscle of the 5th finger to record the action potentials. In control periods they recorded action potentials which had an amplitude of 11 millivolts. An injection of 5 mg acetylcholine was made into the brachial artery, and this had the effect of reducing the amplitude of the action potentials to 2 millivolts about 8 seconds later. These action potentials then recovered their original height after about 8 seconds more. So far the observations were in accordance with expectation. However, about 1 minute after the injection a second reduction in the size of the action potentials was seen. This late depression was greatest about 5 to 10 minutes after the injection when the action potentials fell to 7.5 millivolts. Full recovery from this late depression was not seen until 30 to 60 minutes after the injection.

When acetylcholine is injected it is split into acetic acid and choline. Grob, Johns and Harvey, therefore, wondered whether the late depression was due to one of these two substances. They found that a similar effect was in fact produced by the intra-arterial injection of choline in amounts from 5 to 30 mg, and this result suggested that the late depression after the injection of acetylcholine was caused by the choline set free. They further observed that both the early and the late depression were increased in depth and were prolonged by neostigmine, as would be expected if the depression was due to a depolarizing block, such as acetylcholine or choline would produce.

This evidence of an effect of choline is surprising, because the pharmacological action of choline is low, being only one-thousandth of that of acetylcholine. However, in these experiments large amounts of acetylcholine (5 mg upwards) were injected, and it appeared that the choline when set free by the cholinesterase was sufficient to produce an effect of its own. It is clear that the amounts of suxamethonium ordinarily injected which are 50 to 75 mg might have a similar effect, and thus cause a partial neuromuscular block long after the suxamethonium itself had been destroyed by cholinesterase. When the amounts of suxamethonium injected are considerably in excess of 75 mg, when, for example, they are as much as 400 mg or 1 gramme, the partial neuromuscular block due to the choline might verge

on a complete block, sufficient to account for the slow return of normal respiration which has been observed. Thus difficulties with suxamethonium are not necessarily due to a deficiency of cholinesterase in the patient, or to a failure to break suxamethonium down. The difficulties may be attributed to the choline set free when the breakdown has been achieved. They may be expected to be serious only when large amounts of suxamethonium have been used.

Neostigmine-resistant curarization. When d-tubocurarine has been used to produce relaxation, anaesthetists have met patients in whom this relaxation has not been antagonized or has been poorly antagonized by neostigmine (Prostigmin), with the result that the patients did not start breathing again (Hunter, 1946). One of the suggestions which has been made to explain the failure is that the plasma potassium may have been abnormally low, but this was not always true.

The action of neostigmine in neutralizing the effect of d-tubocurarine or of gallamine can be increased by the simultaneous administration of ephedrine by the intramuscular route. The effect of ephedrine on muscular contraction was first observed by Edgeworth (1930) who found by accident that tablets of ephedrine reduced the symptoms of myasthenia gravis. From 1930 to 1935 ephedrine was regularly used in the treatment of myasthenia, and then after Walker's work (1935) showing the beneficial effect of neostigmine together with atropine, ephedrine was dropped. Various workers (Viets and Schwab, 1939; Schlezinger, 1940; Wilson and Stoner, 1944) stated, however, that the combination of ephedrine with neostigmine was more effective than neostigmine alone.

In 1942 it was demonstrated that the effect of neostigmine on the normal muscle of the cat was potentiated by adrenaline, and also that small amounts of adrenaline which were too small to produce potentiation became effective after the injection of ephedrine (Bülbring and Burn, 1942). The action of ephedrine in the body is generally believed to be due, at least in part, to its action in diminishing the rate of destruction of adrenaline and noradrenaline. The effect of ephedrine on muscular contraction is presumably explained in this way, since it has been shown that adrenaline lowers the threshold for excitation at the neuromuscular junction. It has, indeed, long been known that adrenaline has an anticurarizing action.

The suggestion which emerges is that patients in whom neostigmine fails to exert its usual effect in hastening recovery from curarization should be given, as well as neostigmine, an intramuscular injection of 30 to 60 mg ephedrine. Such an injection might also be beneficial if the failure of the muscle to recover is due to a loss of muscle potassium, for there is some evidence that adrenaline assists the mechanism which maintains the high potassium level of the muscle fibre (Sugimoto, 1932; quoted by Fenn, 1940). Adrenaline certainly has this action in smooth muscle (Born and Bülbring, 1956). The injection of ephedrine would also raise the blood pressure.

GANGLION-BLOCKING AGENTS

Two kinds of action. The connection between the preganglionic and the postganglionic fibres of the sympathetic system is in many ways similar to the neuromuscular junction. The preganglionic fibres liberate acetylcholine and the acetylcholine stimulates the cells of the postganglionic fibres by neutralizing the charge on the cell membrane. Nicotine has a similar action to acetylcholine, and so has the substance tetramethylammonium; the related substance tetraethylammonium, however, has no stimulant action, but it prevents stimulation of preganglionic fibres from being effective, and thus is a ganglion-blocking substance (Burn and Dale, 1915).

The most widely studied ganglion-blocking agent has been the substance hexamethonium, which is chemically similar to decamethonium with the difference that its chain contains six and not ten CH_2 groups. However, although hexamethonium is thus related to decamethonium, it acts on the sympathetic ganglion in a manner different from that in which decamethonium acts at the neuromuscular junction. Hexamethonium prevents the transmitter from acting at the ganglion by competing for the receptors with which the transmitter unites, just as d-tubocurarine acts at the neuromuscular junction. Hexamethonium does not depolarize the ganglion as decamethonium depolarizes the motor end plate.

An effect like that of decamethonium is, however, produced in the ganglion by large doses of tetramethylammonium.

Nicotine has now been shown to act in both ways; small amounts injected into the artery leading to the ganglion block transmission initially by depolarizing, and later by competition.

Action of anticholinesterases. Since hexamethonium acts on the ganglion as d-tubocurarine acts at the neuromuscular junction, it would be expected that neostigmine would antagonize the action of hexamethonium. Actually, it does not do so, and this fact establishes an important difference between the ganglion and the motor end plate in skeletal muscle.

Relation of ganglion to neuromuscular junction. The substance gallamine has a benzene ring to which three identical side chains are attached. Its action has been compared with a second compound differing in the possession of only two of these side chains, and with a third compound differing again in the possession of only one of these side chains. The action of these substances in causing block at the neuromuscular junction was in the ratio of 100 to 25 to 2. Their action, on the other hand, in causing block in the sympathetic ganglion was in the ratio of 2 to 20 to 100 (Bülbring and Depierre, 1949). This gradation of potency in opposite directions suggested that the differences in the physiological mechanism at the two sites are quantitative rather than qualitative. Paton (1954) has pointed out that the great anatomical differences are sufficient to account for dissimilarities in their reactions to drugs.

Route of administration. Ganglion-blocking agents when used in the treatment of hypertension have been given orally and also by intramuscular injection. Their effect when given by mouth has been found to be irregular, and attended by dryness of the mouth as well as constipation. In some patients paralytic ileus has occurred. To prevent these effects pilocarpine nitrate, also taken by mouth, has been recommended (Gunn and Cooke, 1954), for pilocarpine causes salivation and increased intestinal movements by an action peripheral to ganglia.

The irregularity of the action on the blood pressure has been attributed to irregular absorption, and much better results have been obtained by intramuscular injection, using doses sufficient to oblige the patient to lie down for 2 hours after receiving the injection (Harington, 1953).

The substances hitherto used as ganglion-blocking agents have been quaternary ammonium compounds, and all of these are known to be absorbed with difficulty from the alimentary tract. Recently, however, the substance Mecamylamine has been introduced which is not a quaternary ammonium compound, but is a secondary amine. Because of this, Mecamylamine is well absorbed by mouth, and the blood pressure can therefore be controlled with success when it is given by mouth. However, it causes side effects similar to those recorded for hexamethonium. Its action is prolonged and the effect of one dose may last for 12 hours or more. It is perhaps worth noting that the simplest method of restoring the blood pressure, should this have become too low as a result of using a ganglion-blocking agent, is to inject ephedrine by the intramuscular route. Its effect is exerted peripherally and is not dependent on nervous impulses, but it should not be repeated at intervals much less than one hour.

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BOOK REVIEW

Recent Advances in Anaesthesia and Analgesia (including Oxygen Therapy) (8th edition). By C. Langton Hewer and J. Alfred Lee. Pp. 295; illustrated. Price 40*s*.

One has looked forward to the appearance of this new edition of " an old friend ". To all intents and purposes this is a new book, only the chapter on oxygen therapy bearing any real resemblance to its forebear in the earlier editions. Dr. Langton Hewer in his preface states that he has made it a working rule to include " only developments which have taken place in the past few years ", but to make exceptions in regard to some new topics " sufficiently recent to be dealt with as a whole ". Among these latter are Muscle Relaxants, Induced Hypotension and Hypothermia, Phenothiazine Derivatives, and Anaesthetic Explosions.

This is an excellent compendium of advances in the technological field, but no attempt is made to review recent work on the basic principles of anaesthesia. More surprising perhaps is the absence of any reference to the management of patients with respiratory inadequacy or in coma, except for a brief reference to the influence of this work on the design of apparatus.

In the new chapter on relaxants the advice given as to technique is conservative. It is surprising still to find recommended doses of tubocurarine as low as 10–15 mg. The omission of much of the new work on basic aspects of the actions of these drugs must be regarded as a weakness in this review of the subject.

Two features lay the new publication open to criticism. There has obviously been insufficient care taken in regard to the references. Even a casual reading has revealed wrong names of authors, wrong page numbers and inadequate detail—e.g. on page 118, " Cole, L., 1934 and 1935, *Lancet* ". Secondly there is considerable confusion in the unpredictable use of proprietary and approved names for drugs. The use of " trilene " may be permitted by virtue of its familiarity, but the use of " marzine " followed in parentheses by the approved name " cyclizine " coupled with a further proprietary name " marezine " can only confuse, and this is only one example of many similar instances. The editors missed an opportunity to assist prospective authors by indicating clearly approved names for new remedies.

Useful, if not invaluable, to teachers and students, the new edition follows the tradition established by its forerunners and will fill the same need.

T. Cecil Gray

Brit. J. Anaesth. (1957), **29**, 249

THE ASSESSMENT OF RELAXATION IN MAN

BY

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INTRODUCTION

"RELAXATION" is a clinical term used in the field of anaesthetics to describe a state in which the usual reflex motor responses to sensory stimuli are absent or depressed. In the circumstances of present day clinical anaesthesia, or those of experimental studies, the observation that such a state is present is generally not in itself sufficient. Some quantitative estimate of the extent or degree of relaxation is also needed. The anaesthetist then has more accurate knowledge of, for example, the depth of general anaesthesia or, in the case of one of the specific relaxant drugs, the intensity of its effect and whether and when further doses are necessary. The ability to assess with some accuracy the degree of relaxation makes it possible to investigate the relaxant effects of a drug and to plot such important graphs as the effect-time and the dose-effect relationships, and to determine the duration of any particular effect of the drug for a given dose.

In this paper we set out the general principles and types of methods on which the assessment of relaxation may be based. This is followed by illustrated examples drawn from the literature.

Relaxation results from an interruption, partial or complete, of the nerve pathway between the site of a sensory stimulus and the motor end plate. The interruption may be at the following sites:

(*a*) At the myoneural junction. This is the site of action of the common relaxant drugs like d-tubocurarine, gallamine and suxamethonium. However, general anaesthetics also affect the myoneural junction to varying degrees (fig. 1).

(*b*) The efferent pathway, i.e., the motor nerve. Nerve blocks and spinal analgesia all prevent the motor impulse from reaching the muscle, and relaxation therefore results from these procedures.

(*c*) Central. General anaesthetics act on the brain and spinal cord depressing cells and synapses.

(*d*) The afferent pathway, i.e. the sensory nerves and nerve endings. Nerve blocks, spinal analgesia, infiltration anaesthesia and topical anaesthesia all produce relaxation by an interruption at this site.

In general, relaxant action is studied by the application of a stimulus, the magnitude of which is controlled, and the measurement of the muscular response. Where the stimulus is applied and where the response is studied determines which single site or group of sites is tested for the action of the drug in question. There is an interesting addition to this general rule. For assessing the relaxant action of the depolarizing drugs, the depolarization voltage can be directly measured (fig. 14). This would provide one means of elucidating the mode of action of a relaxant drug acting at the periphery, as well as relating effect to dose in the case of a depolarizing relaxant.

GENERAL PRINCIPLES OF ASSESSING RELAXANT ACTION OF ANY DRUG

1. *For single dose administration.*

For a complete investigation, the intensity of effect, as shown by the reduction in magnitude of some muscular action, is recorded continuously throughout the period of action of the drug. Respiration may, for example, be chosen as the muscle activity to be observed. From a spirometric recording the minute and tidal volumes are determined which give a quantitative indication of the activity of the respiratory muscles (figs. 2, 3, 12). In other cases the magnitude of a muscular contraction, when its motor nerve is stimulated electrically, may be measured at regular frequent intervals (figs. 8–12).

As a result of continuous observation and measurement, two important characteristics of the drug action can be extracted.

(*a*) The intensity of the peak effect of the dose given.

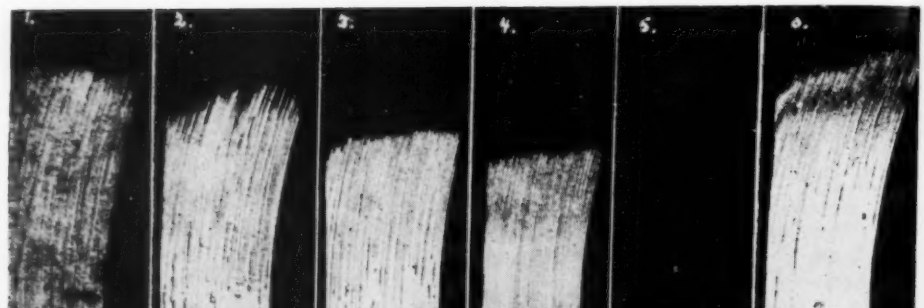

FIG. 1

The effect of ether anaesthesia on neuromuscular transmission in a rabbit. Electrical stimuli were applied to the cut sciatic nerve at a frequency of 1.5 per sec and the contractions of the leg were recorded mechanically. The traces show the magnitudes of the contractions (1) in a waking animal, (2) after 3 per cent ether for 30 min, (3) after 5 per cent for 30 min, (4) after 5 per cent for 60 min, (5) after 6 per cent for 30 min, and (6) 60 min after shutting off the ether. It is seen that ether had a pronounced effect on the neuromuscular transmission. In the same paper the authors demonstrate that the neuromuscular block due to ether, like that due to d-tubocurarine, is reversed by neostigmine. (Poulsen and Secher, 1949)

(*b*) The duration for which the effect of the drug exceeds some certain value. By selecting some easily observed limit such as the presence of apnoea or, in the conscious volunteer, the presence of diplopia or the inability of the subject to, say, snap his fingers, this duration can be determined without the need for continuous recording.

2. *For continuous administration e.g. intravenous drip or by inhalation.*

(*a*) Here again the action may be studied by recording the intensity of the effect continuously while at the same time noting the rate of administration of the drug from moment to moment.

(*b*) If, however, the rate of administration is held constant, a steady state of relaxation is eventually reached (fig. 4), and the intensity of this effect can then be determined by one of the methods to be mentioned.

(*c*) The rate of administration may be so regulated that it just produces a given effect. This is a method which is in common use by many anaesthetists who use suxamethonium continuously throughout an operation, in the form of an intravenous drip of dilute solution. This technique has been referred to as a " titration of the patient " with suxamethonium, so that apnoea is just not produced. Apnoea is here regarded as an end point which, if reached, indicates that the drip should be slowed or stopped.

THE RESPONSE TO STIMULI

Were it practical, a study of the magnitude and frequency of the action potentials in the motor nerves themselves would give some valuable quantitative indication of stimuli travelling to their muscles. Such observations might then be correlated with others in determining, for example, how much of any relaxant effect was due to central

and how much to peripheral action. If it were desired to assess the degree of relaxation produced by a centrally acting drug when a peripherally acting drug was being administered at the same time, this method would be the only direct one. However, in human subjects this is not practicable since it is generally impossible to expose the motor nerves.

The motor response in some muscle or group of muscles may be studied. This is done by one or more of the following methods:

(*a*) By recording the action potentials developed in the muscle when it contracts (electromyography). These potentials can be picked up by surface electrodes or by the insertion of fine needle electrodes into the muscle. A suitable amplifier enables them to be either displayed on a cathode ray oscilloscope or recorded on a pen writer. With a surface electrode the activity of most of the muscle is recorded. The integrated electrical output has been shown to be proportional to the tension developed by the muscle in voluntary contraction but not in electrically stimulated contractions (Lippold, 1952). With a needle electrode the activity of a small number of muscle fibres is recorded selectively (fig. 12).

(*b*) The force of contraction of a muscle can be measured mechanically.

(i) Directly—by measuring the pull of the muscle in an isolated nerve-muscle preparation. This can only be done in animal experiments.

(ii) Semi-directly—by measuring the pull of a limb or a group of muscles (figs. 8, 9).

(iii) Indirectly—by observing some, generally compound, muscular function, such as respiration, snapping of finger and thumb, speed of knitting or putting pegs into holes.

THE STIMULUS

There are four main types of stimulus, which can be used in assessing relaxation.

1. *Stimuli which occur normally.*

(*a*) *To the respiratory muscles.* Spirometric recordings are taken throughout the period of action of the drug and, from these, such data as the tidal volume and minute volume can be obtained from moment to moment (figs. 2, 3, 12). In conscious subjects, however, respiration may be a poor guide to relaxant action because apprehension may cause alterations in respiratory rhythm and volumes.

(*b*) *To the jaw muscles.* In conscious volunteers the stage at which the subject cannot hold up his jaw forms a convenient end point. In unconscious patients the "tightness" of the jaw muscles can generally be fairly accurately gauged by an experienced anaesthetist and is commonly used as a guide either to relaxation or to depth of anaesthesia.

(*c*) *To the eye muscles.*

(i) Diplopia is easily appreciated subjectively by a conscious volunteer and forms a very delicate means of detecting the presence of even small degrees of relaxant effect. The disappearance of diplopia is a valuable end point for determining the duration of effect. When diplopia disappears the relaxant can be said to have ended its main action.

(ii) The width of the palpebral fissure with the subject in repose can be measured and is a very useful adjunct to other observations. It is, however, liable to some subjective interference.

Observations such as these give information about the effect-time and dose-effect relationships both in the case of central and in that of peripheral relaxant action. Many of these methods are commonly employed during general anaesthesia for assessing relaxation.

2. *Voluntary stimulation.*

Here, the conscious subject makes various muscular movements at request.

(*a*) *Grip strength.* To measure this a variety of dynamometers have been constructed. The subject compresses a spring by his handgrip or squeezes a rubber bulb connected to a manometer. The compression or pressure developed is measured (figs. 6, 7).

(*b*) *Contraction of the abdominal muscles* against a spring in a suitably constructed dynamometer (figs. 5, 6, 7).

(*c*) *Leg thrust.*

(*d*) *Expiratory effort*—measured by observing the pressure difference produced across an orifice when blowing through it with maximum effort or by blowing into a closed chamber and measuring the pressure developed.

(*e*) *Other respiratory measurements,* e.g. vital capacity and maximum ventilatory effort.

(*f*) *The strength of the jaw muscles* can be gauged by biting on a suitable dynamometer.

(*g*) *The width of the palpebral fissure* with the subject making a maximum effort to open the eyes, can be measured.

Clearly these observations can only be made on conscious subjects and are thus restricted to the assessment of the relaxant action of drugs which act at the periphery or directly on nerves.

3. *Direct electrical stimulation of a motor nerve.*

In this method the stimulus is applied, usually to the ulnar or median nerve, the response being observed in the muscles actuating the fingers or thumb. Such a method may occasionally be inconvenient during clinical anaesthesia, but apart from this limitation, the method measures peripheral relaxation uniquely and, carefully carried out, can give reliable and accurate results (figs. 8–12).

4. *Other applied stimuli.*

The main example in this group is that of surgical stimuli. The response may be observed, for example, in the form of limb movements, tightness of the abdominal muscles (fig. 13), the muscles of the eyelids and those of the jaw. These effects can rarely be measured with any accuracy, though experienced anaesthetists can form a very useful estimate of relaxation from them. Another example of an applied stimulus is that of the anaesthetic vapour or of an endotracheal tube on the laryngeal or tracheobronchial mucosa. The production or absence of a cough or of adduction of the cords when they are stimulated in this way is a convenient and fairly well defined end point for observation.

A combination of the last two types of stimulus is utilized by pharmacologists for differentiating between centrally and peripherally produced relaxation. The knee jerk is recorded and the magnitude compared with that obtained by direct stimulation of the sciatic nerve. A depression of the magnitude of the knee jerk, when there is no similar depression in the magnitude of the contraction of the calf muscles on electrical stimulation of their motor nerves, clearly indicates a depression of the spinal cord synapses.

While tendon reflexes during anaesthesia have been studied (Brown, 1955b), the combination of tendon reflex elicitation and electrical motor nerve stimulation does not appear to have received much attention as a method of studying relaxation in man.

EXAMPLES OF METHODS

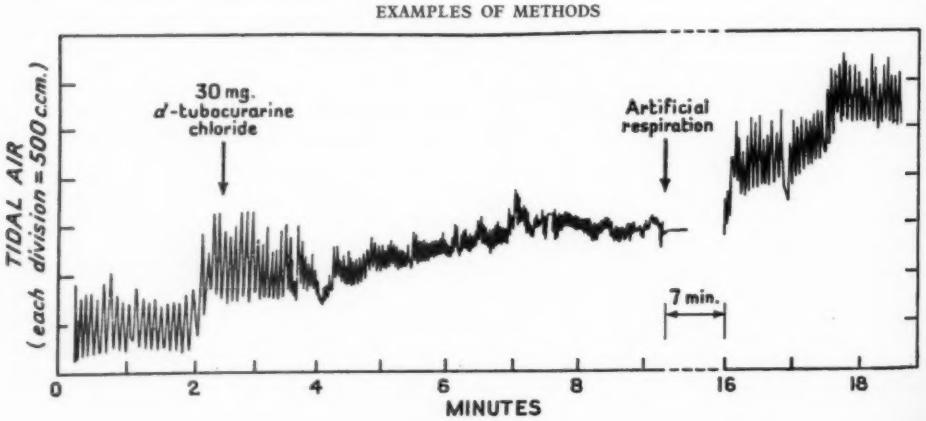

FIG. 2

Spirometer tracing taken from a conscious subject during the intravenous injection of 30 mg of d-tubocurarine chloride. It shows the reduction of tidal volume from 750 to 115 ml over a period of 5 min, and an increase in respiratory rate from 11 to 50 per min, before artificial respiration was instituted. The duration of action of the relaxant was shortened by the intravenous injection of 1.5 mg of neostigmine. From a tracing of this sort, an effect-time graph can readily be plotted. Values for either minute volume respiration or tidal volume, at regular intervals, may be determined from the tracing. (Prescott, Organe and Rowbotham, 1946)

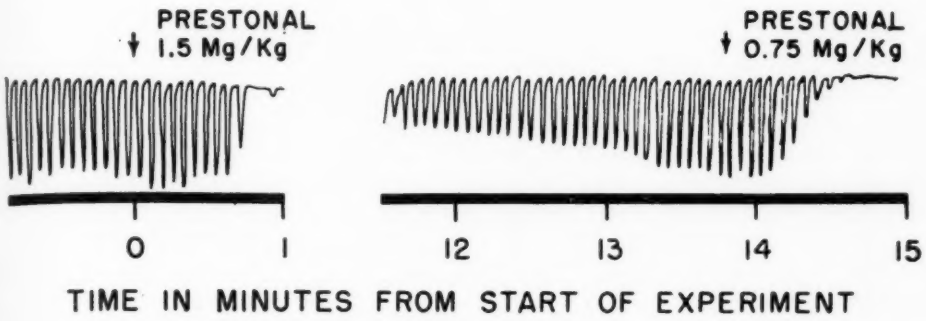

FIG. 3

Spirometer tracing obtained from an anaesthetized patient. It shows the rapid production of apnoea soon after the injection of the relaxant (1.5 mg Prestonal per kg body weight), the subsequent gradual return to normal and the recurrence of apnoea after a further smaller dose of the relaxant. (Rendell-Baker, Foldes, Birch and d'Souza, 1957)

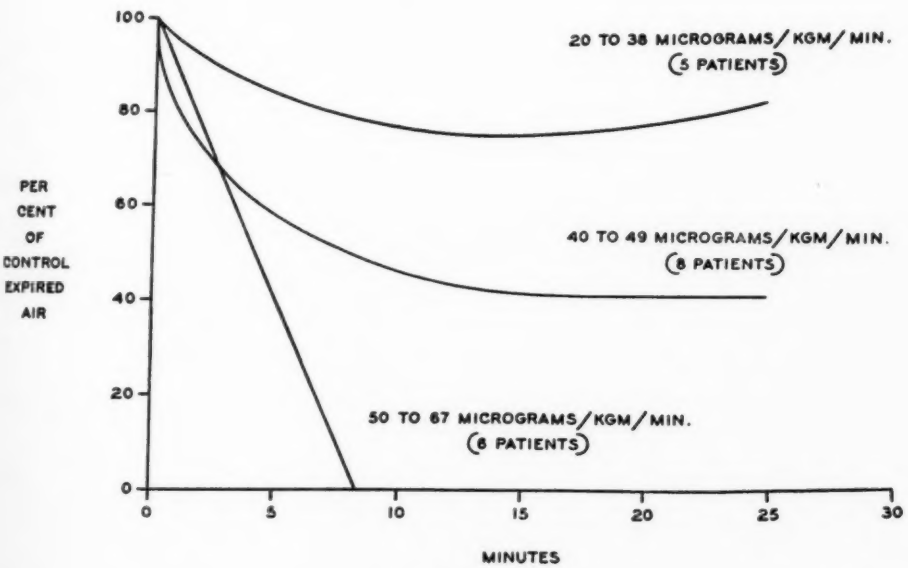

FIG. 4

Averaged effect-time curves for continuous infusion of a relaxant, suxamethonium, in patients anaesthetized with cyclopropane and ether. In the graph the ordinate gives the minute volume respiration as a percentage of the normal, and is taken to indicate the degree of relaxation. The curves for the two smaller rates of injection show how a stable degree of relaxation is established after a time. The biggest rate of injection is more than enough to produce apnoea. (Espinosa and Artusio, 1954)

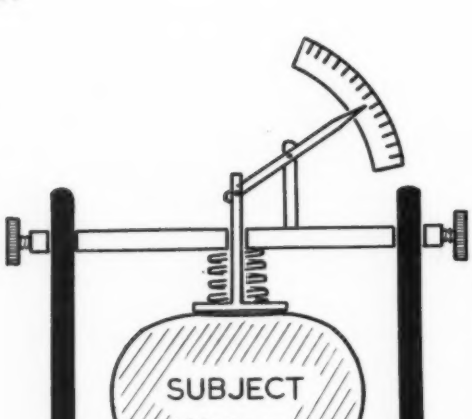

FIG. 5

Assessment of relaxation in conscious subjects by means of voluntary contraction of the abdominal wall. The subject lies supine with thighs firmly strapped down. A spring loaded pad just bears lightly on the centre of the recti abdominis muscles. On the command "raise your legs" the recti become taut and the pad is pushed up against the spring which moves a pointer over a scale. A similar spring and pointer arrangement was used for measuring the flexing power of the fingers.

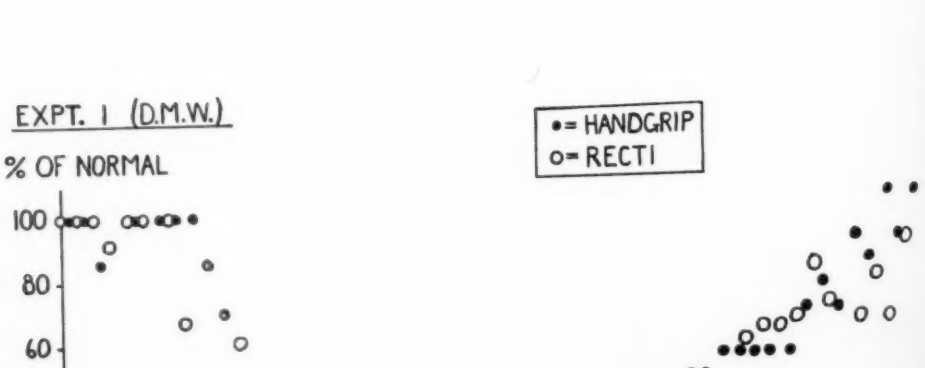

FIG. 6

This graph was obtained in a volunteer who received gallamine triethiodide intravenously. The responses of the finger and recti abdominis muscles are plotted in terms of percentage of normal against time. It is seen that the response falls fairly rapidly to zero and then slowly recovers. (Mushin, Wien, Mason and Langston, 1949)

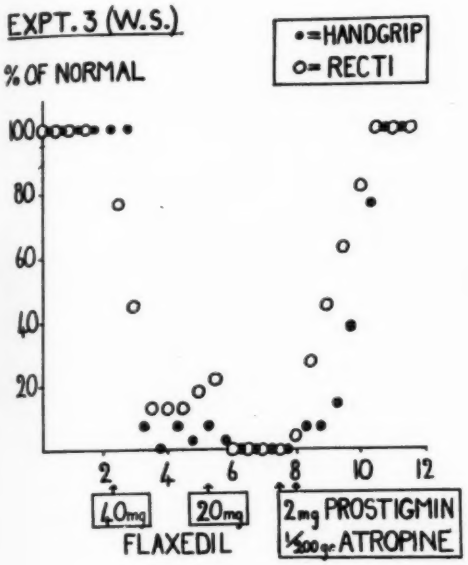

FIG. 7

A record of a similar procedure to that in figure 6 in another volunteer in which the response returns rapidly to normal after the administration of neostigmine. (Mushin, Wien, Mason and Langston, 1949)

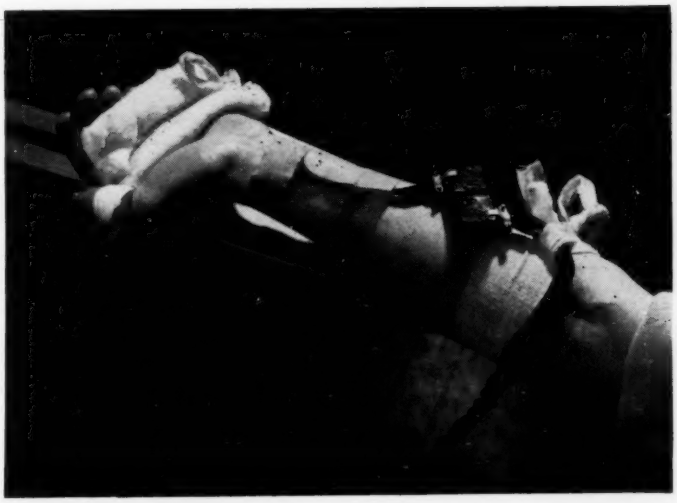

FIG. 8

An example of the electrical stimulation of a motor nerve with mechanical recording of the tension developed in the muscle. The detail of the stimulation site is shown. The multiwick stimulating electrode is held in place at the wrist with a length of strapping. The neutral electrode consists of the metal armrest with a saline soaked pad on it. This is concealed below the upper part of the forearm. Bandages hold the arm firmly in position. Submaximal tetanic stimulation is used and consists of bursts of pulses, each 9 m.sec wide, at a frequency of 50/sec. The bursts last for 1.2 sec and are repeated every 6 sec. The tension developed in the short muscles of the thumb is transmitted to the recording mechanism via the leather strap and a wire. (Mapleson and Mushin, 1955)

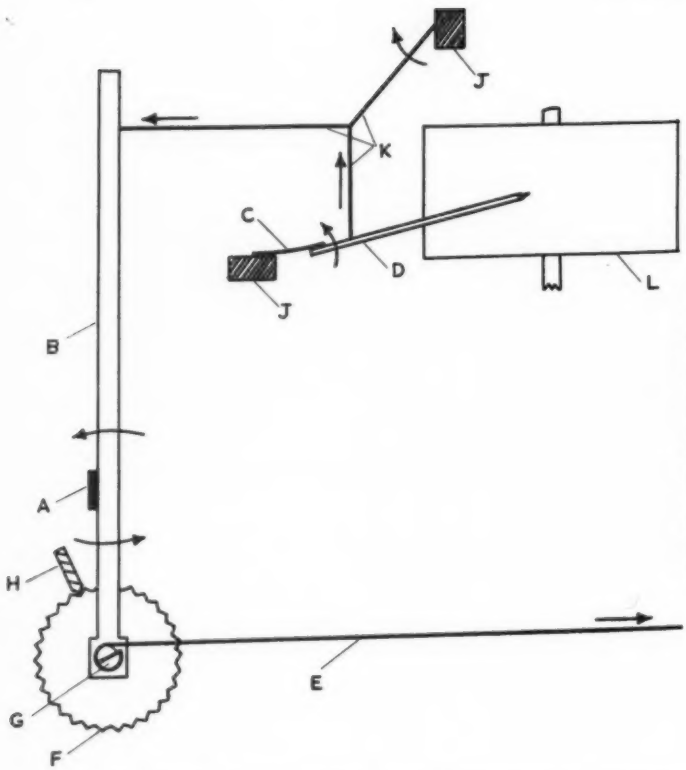

FIG. 9

Diagrammatic representation (side view) of the recording system to which the subject in figure 8 was connected. The tension from the thumb muscles is transmitted along the wire E so rotating the lever B about the torsion bar A (A provides a frictionless bearing for B, and forms the main spring against which the muscle pulls). JJ are fixed points so that the strings K transmit the movement of the top of lever B to the pen arm D. A frictionless bearing for D is provided by the brass strip C. L is the recording drum. FGH form a device for adjusting the resting tension in the wire E. (Mapleson and Mushin, 1955)

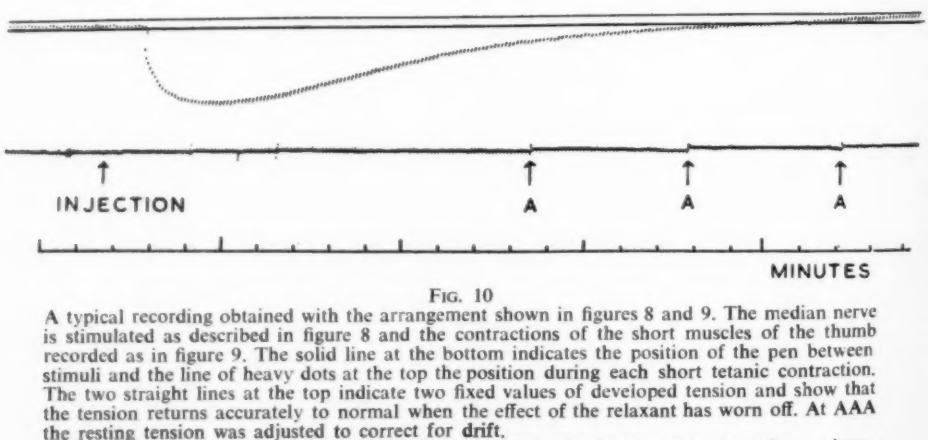

FIG. 10

A typical recording obtained with the arrangement shown in figures 8 and 9. The median nerve is stimulated as described in figure 8 and the contractions of the short muscles of the thumb recorded as in figure 9. The solid line at the bottom indicates the position of the pen between stimuli and the line of heavy dots at the top the position during each short tetanic contraction. The two straight lines at the top indicate two fixed values of developed tension and show that the tension returns accurately to normal when the effect of the relaxant has worn off. At AAA the resting tension was adjusted to correct for drift.

The recording shows a peak reduction of 75 per cent in the developed tension after an intravenous injection of 0.53 mg gallamine triethiodide per kg body weight. (Note: the pen deflections in the recording are not linearly related to developed tension.) (Mapleson and Mushin, 1955)

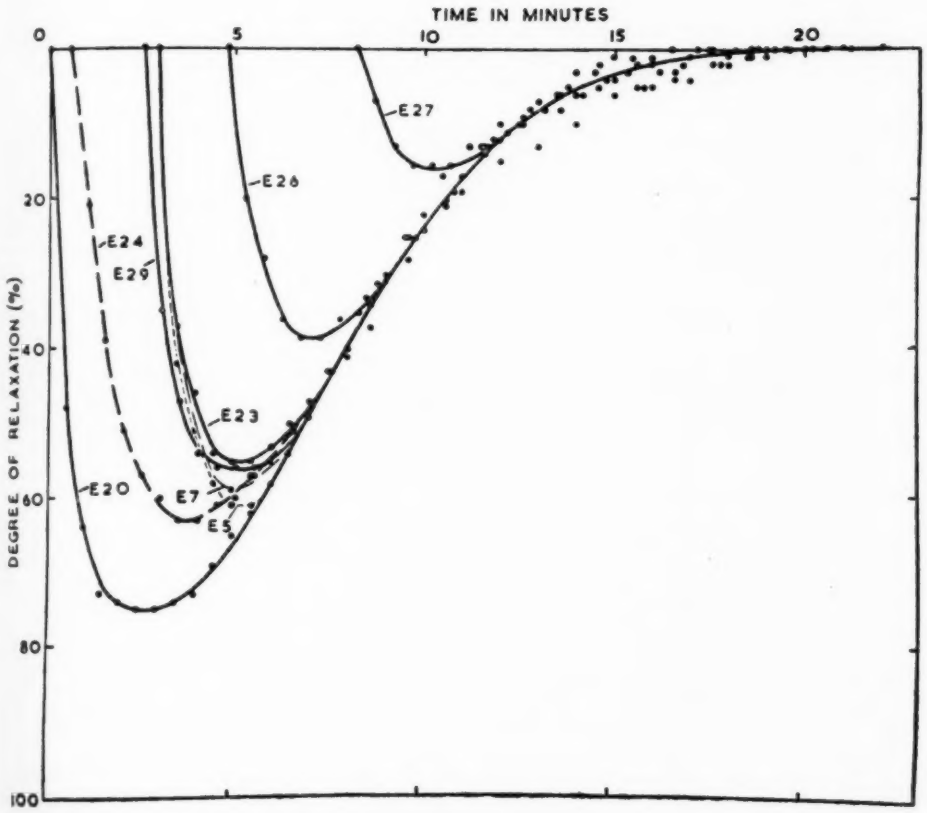

FIG. 11

Eight effect-time curves from one subject derived from recordings as shown in figure 10. The curves have been superimposed in such a way that their "tails" coincide and it can be seen that the "heads" of the curves form a fairly systematic pattern. (Mapleson and Mushin, 1955)

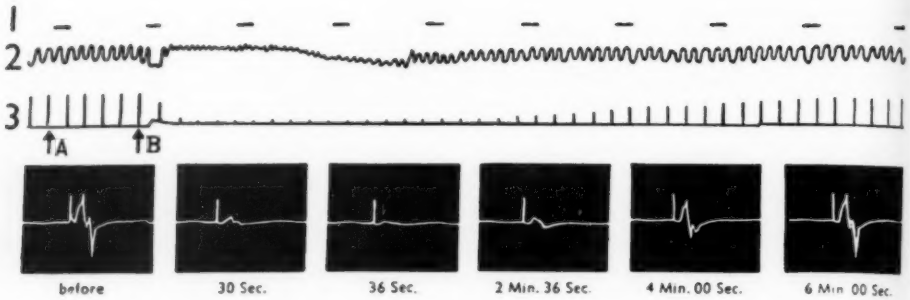

FIG. 12

Simultaneous recordings in a conscious subject of respiration (trace 2) and electrically stimulated contraction of the flexor muscles of the fingers—recorded both mechanically (trace 3) and electromyographically with a concentric needle electrode (lower pictures). The stimuli were submaximal and consisted of 1 m.sec pulses applied at 6 sec intervals to the median nerve. Trace 1 shows time marks at half-minute intervals. From A to B 24 mg of suxamethonium diiodide were injected intravenously. In the electromyogram the initial upward spike is an artefact produced by the stimulus; the subsequent deflections of the trace are the true muscle action potentials. The times given below the electromyograms are measured from point A.

It can be seen that all three activities are rapidly reduced to near zero and then slowly return to normal. However, they do not follow an exactly parallel course. At B, for instance, 30 sec after A, the respiration and finger contraction are still normal but the action potential is greatly reduced. Again, at 2½ min after A, the tidal volume is back to about three-quarters of normal while the finger contraction is only about one-quarter of normal. (Hougs, Poulsen and Sonne, 1952)

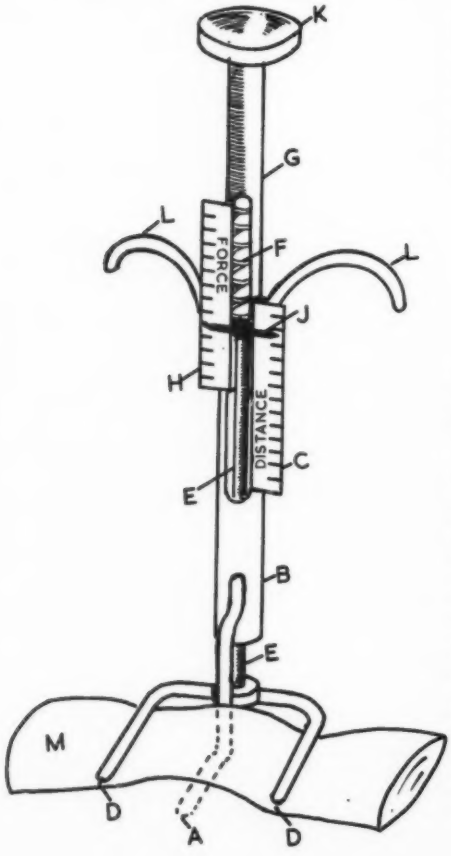

FIG. 13

An instrument which we have designed for the assessment of relaxation of the abdominal muscles during a laparotomy. The central prong A is fixed to the outer barrel B (to which scale C is attached). The two outer prongs DD are fixed to rod E which is linked, via spring F, to the inner barrel G (to which scale H is attached). The double pointer J is fixed to the top of rod E. Thus scale C indicates the movement of prong A relative to prongs DD, while scale H records the compression of spring F and hence the force drawing prongs A and DD together.

With the thumb on button K and the index and middle fingers round hooks LL the instrument is inserted into the laparotomy wound so that the recti muscle lies between the prongs A and DD. Button K is gently pressed down until contact is just made between all three prongs and the muscle, and the scale readings noted. Button K is then pressed down further and the scales read again. The differences between the two pairs of readings give the force required to distort the muscle by a given amount. This is clearly some function of the tone of the muscle and so gives an objective quantitative measurement of relaxation, which may be preferable to the subjective impression of "tightness" gained by the surgeon with his fingers.

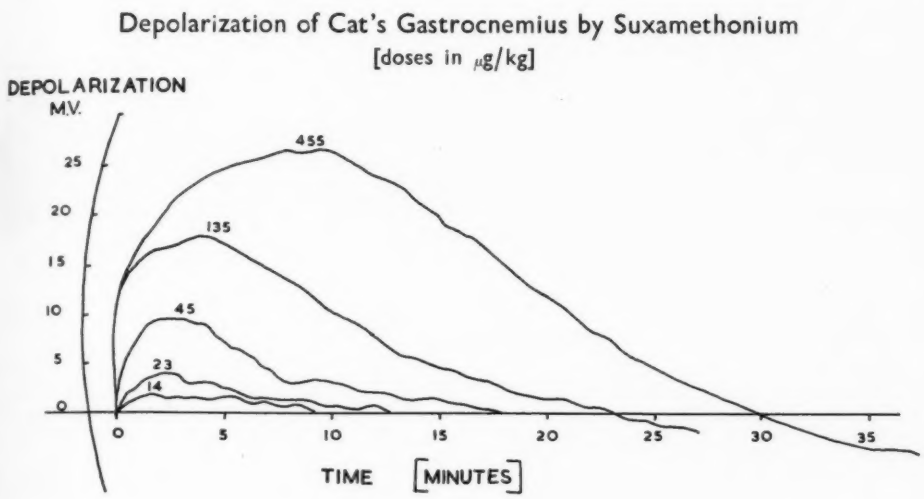

FIG. 14

This record shows the magnitude of the depolarization voltage resulting from various doses of suxamethonium. These curves were obtained from a cat anaesthetized with chloralose. The electrodes, with the interposition of small saline-filled cotton wool swabs, were placed on the muscle without attempting to localize the end plate regions. (Paton, 1956)

CONCLUDING REMARKS

The investigator or clinician will find that in any particular circumstance only some of these methods are practical or likely to give useful data. His choice will necessarily be conditioned, not only by the difficulties of making certain measurements in an operating theatre during a surgical operation, but also by the accuracy which he seeks, and the limitations on accuracy imposed by the different methods. Measurements of voluntary contractions cannot be made during anaesthesia and even in trained conscious volunteers their accuracy is limited to that with which the subject can reproduce a given effort. Apprehension on the part of conscious subjects may also introduce serious errors, particularly when respiratory recordings are being taken. The effects of autogenous adrenaline in altering the action of competitive blocking agents must also be taken into account (Paton and Zaimis, 1950). For the most accurate results, stimulation of the motor nerve and recording either the muscular contraction or the muscle action potentials is almost certainly the best approach. Accuracy of the order of a few per cent can be expected.

In utilizing results obtained from any one of these methods it should be borne in mind that different muscles may exhibit different degrees of relaxation at the same moment. It is important, therefore, in comparing results that the same conditions be always present. Another way in which some confusion might arise when comparing drugs is that different results may be obtained with different methods. Thus figure 12 shows that in the case of a particular dose of a relaxant, the effect-time and the dose-effect relationships varied according to whether the assessment was made by observation of respiratory activity, contraction of a muscle in response to an applied stimulus or the electromyogram.

Even when highly developed techniques are not readily available, the anaesthetist possessing experience and clinical acumen can still use some of the other methods we have described to make worthwhile, roughly quantitative, observations which will enable him to form a very valuable and useful assessment of relaxation.

ACKNOWLEDGMENTS

We should like to express our grateful thanks for the permission which was so readily given to us by the various authors and journals concerned to reproduce illustrations. We are also indebted to E. K. Hillard, L.I.B.S.T., Senior Technician to this Department, for the drawing of figures 5 and 13.

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A Measurement of normal respiration.
B Measurement of the width of the palpebral fissure.
C Measurement of various voluntary movements (handgrip, leg raising, speed of knitting, etc.).
D Measurement of various forced respiratory actions.
E Electrical stimulation with mechanical recording of muscle tension.
F Electromyographic recording.
G Direct measurement of depolarization potentials.

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THE ANAESTHESIA LABORATORY OF THE HARVARD MEDICAL SCHOOL AT THE MASSACHUSETTS GENERAL HOSPITAL

BY

HENRY K. BEECHER

THIS laboratory is 21 years old this year and should by now have "come of age", but it is with some hesitation that I describe (on request) its activities, not because I am fearful that others may pick up leads and pursue them successfully—indeed that would fulfil a major purpose of the laboratory—but because of a natural reticence to describe one's activities in detail to the reader lest he seem to have an exaggerated idea of their significance. Whether or not our excursions into the laboratory have been successful is beside the immediate point. I am impelled to discuss these things because it seems that a sufficient number of investigators, especially young investigators in the field of anaesthesia, do not appreciate what a rich harvest awaits their work.

According to the late Mr. Vincent of the Rockefeller Foundation, "Doctors don't reason: they just rearrange their prejudices." There is no deterrent as good as a laboratory in preventing the easy arrangement of prejudices as a substitute for reasoning. I should like to describe the Anaesthesia Laboratory in terms of what we are doing and where we are heading. While the quality of our teaching may or may not be at once much influenced by the presence of research activities, I am sure it will be in the end. It is quite clear that we have had a better selection of residents to choose from because of these activities. Such considerations are therefore pertinent to an "Educational Number" of this Journal.

A NEGLECTED AREA IN MEDICINE

It is fitting that research in anaesthesia at the Massachusetts General Hospital should be an integral part of the institution, for, as though to celebrate the Hospital's silver jubilee in 1846, Morton's research with a fish, a dog, and one, Gilbert Abbott, produced the hospital's first great scientific contribution—a demonstration that is recognized over the world as a milestone in the progress of civilization. Notwithstanding its auspicious introduction into clinical medicine, anaesthesia as a field for scholarly study remains a neglected area.

Some insight into the importance of this neglect can be obtained, perhaps, by taking a look at the results of the study that Beecher and Todd (1954) conducted in ten university hospitals. A careful on-the-spot examination of more than a half million anaesthetic administrations over a five-year period indicated that the death rate associated with anaesthesia (anaesthesia deaths were so designated in each of the ten participating hospitals) is about 1:1650. Curiously, while numerous dissenting opinions were expressed as to the causes of the deaths, no serious challenge was raised of this order of magnitude of deaths in which anaesthesia played a prominent part, taking into account the high proportion of the cachectic, ill and aged in the usual university hospital in this country. While the patient's problems in the university hospital are more serious than the average, so also probably their care is better. One can extrapolate this roughly to cover all of the 7,000,000 anaesthetic administrations carried out in the 160,000,000 population of the United States each year. We then find that twice as many citizens die of anaesthesia as died in this country each year from poliomyelitis in the prevaccine era. When one considers the millions rightly spent each year on poliomyelitis research (and the success achieved) compared with the small sum spent on anaesthesia, the need for giving attention to research in anaesthesia is evident.

GOALS OF THE ANAESTHESIA LABORATORY

Anaesthesia in its death-dealing power is a neurological " disease ". Its sought-after primary effect is, of course, depression of the central nervous system; to an extraordinary extent anaesthetic secondary or toxic effects strike through the nervous system. For example, even a complication apparently unrelated to the nervous system, like the accumulation of fixed acids in the blood as a consequence of ether anaesthesia, can be prevented, as Brewster et al. (1952) have recently shown in dogs by block of the nerve pathways to the adrenal glands. Even when these pathways are blocked, one can clinch the proof by injecting the secretion of the adrenal glands, adrenaline, in physiological amounts and show how this then results in the accumulation of fixed acids in the blood. The key to the understanding of most of the good and the bad powers of anaesthetic agents lies in the nervous system.

There are three goals of the Anaesthesia Laboratory: one is to study the problem of irritability (responsiveness) of the tissues to stimuli and the suppression of this irritability by drugs—as fundamental a problem as exists in all biology; and second—a practical problem—to lower the death rate from anaesthesia. Third, we believe that the thoughtful approach to problems necessary in a laboratory improves our teaching and the conduct of our department.

Let us consider the practical problem for the moment. How can the practical goal best be achieved? One point of view might be to go at once to a study of the complications of anaesthesia: for instance, how often and why does spinal anaesthesia cause severe headache, and why are some paralyses permanent after spinal anaesthesia, as in the cauda equina syndrome? Such studies are needed and they are important; but to attack them is to attack the *symptoms* of the " disease ", not the " disease " itself. In any case, funds are readily available from a number of sources for relatively short-term studies of this kind.

In the long run, far greater distance will be covered and more of lasting value accomplished if a long-range attack can be made upon the basic problem stated in the first goal: study of the primary effects of anaesthesia, study of what the anaesthesia process does, and what anaesthetic agents do to the nervous system in terms of *basic* pharmacology and physiology.

THE BROAD FIELD

Those not previously familiar with our work might wonder at the variety of the attacks being made on the problem at hand. The rationale of this several-phase attack becomes clear when it is realized that what can be studied profitably are the central nervous system depressants as a group. It is customary to divide these up into sedatives, hypnotics (the sleep producers), analgesics (the pain relievers), antitussives (cough suppressors, surely related to the analgesics), ego depressants (agents used in " truth serum ", so-called), and anaesthetics (Beecher, 1957). The needlessness of a rigid preservation of these several categories becomes apparent when it is realized that, for example, nothing more than an increase in dosage of a barbiturate is adequate to take a patient through this gamut from sedative to anaesthetic. A useful cross fertilization of ideas comes from related work in these several categories.

SPECIFIC NEUROPHYSIOLOGICAL STUDIES

I shall describe how we have attacked the problems presented by anaesthetic and related agents, and how we hope to continue, handicapped as we are in planning and in holding research teams together by short-term grants.

(1) *Techniques which make possible a study of the white matter of the central nervous system.* In animals, Rudin and Eisenman (1951) showed in this laboratory that various spinal cord tracts could be easily dissected over lengths of 10–15 cm and removed to a nerve chamber where the character of the action potentials and metabolic peculiarities of central nervous system *white* tissue could be studied for as long as 24 hours. They have shown that these tissue masses are adequately oxygenated by diffusion alone and that spike potential properties are normal. In order to establish the fact of adequate oxygenation, studies were carried out which involved elevated tensions of oxygen. While the point was demonstrated

with tensions slightly exceeding one atmosphere, deleterious effects of the oxygen were encountered at two atmospheres and studied extensively at eight. This led to a series of observations (Rudin and Eisenman, 1952) which demonstrated that "oxygen poisoning" produces changes consistent with increased permeability of the cell membrane with loss of intracellular potassium and accumulation of it in the intercellular area. These techniques can now be applied to a study of the effects of anaesthetic agents on the cell membrane. This is very important. All evidence to date indicates that normal conduction of nerve impulses requires a normal membrane. The fundamental problem is how anaesthetic agents alter membrane properties and thus conduction of nerve impulses. Rudin and Eisenman (1951) have also characterized the normal after-potential sequence of this tissue and have found it strikingly different from that of peripheral nerve, notwithstanding many assumptions by others to the contrary. Associated with this difference there are some very interesting special responses of this tissue to altered ionic environment. This revolutionary new technique makes available a new class of neural tissues (white matter) for electrical and pharmacological study of the effects of anaesthetic agents on the central nervous system.

(2) *Study of the electrical activity of the central nervous system in sleep and in wakefulness and as influenced by anaesthetic agents.* Brazier's (1951) work in this laboratory on the effects of barbiturates on the electrical activity of the brain; in particular, her demonstration that with the onset of sleep the origin of the electrical activity shifts from the occipital to the frontal region (Brazier, 1949); her new method of measuring depth of sleep, and the effect of hypnotic agents upon this, as well as the work (Brazier and Beecher, 1952) on motility during sleep and the effects of drugs on this, are all fundamental attacks upon the basic problems of the primary effects of the central nervous system depressants.

(3) *Work on the mechanism of pain relief.* Other work in this laboratory on animals (Beecher et al., 1939) laid the basis for our current explanatory hypothesis as to how barbiturates in small doses can block pain in man (Keats and Beecher, 1950), presumably by block of internuncial neurones, producing a temporary, reversible, pharmacological lobotomy. (The similarities of this state with surgical lobotomy are striking). This hypothesis (loc. cit.) needs further study as a basic approach to an understanding of the mechanism whereby pain can be relieved. We have made the assumption that full perception of the experience of pain requires intact association paths, long circuiting, reverberating nerve impulses, intact internuncial neurones, to put it into neurophysiological terms.

(4) *The neurological control of respiration.* In work interrupted by World War II, Beecher and Moyer (1941) studied the mechanisms of respiratory failure under barbiturate anaesthesia and, in particular, the variability of the Hering-Brewer reflexes under barbiturates (Moyer and Beecher, 1942a). Central stimulation of respiration by anoxia was also demonstrated, apparently for the first time (Moyer and Beecher, 1942b). Study then was directed at the cellular level to the effects of oxygen tension on the metabolism of cerebral cortex, medulla and spinal cord (Craig and Beecher, 1943a), and to the effect of low oxygen tension on tissue metabolism (Beecher, et al., 1942; Craig and Beecher, 1943b). High oxygen tensions were studied at toxic levels in Drosophila (Williams and Beecher, 1944). These basic studies led easily to practical studies of the respiration described below in the section on metabolic problems. Practical procedures of anaesthesia for thoracic surgery were summarized by Beecher (1951).

(5) *Circulatory changes.* Early circulatory studies began with changes in brain volume produced by anoxia and hypercapnia during anaesthesia (White et al., 1942) and progressed to a study of lymph formation and flow (Beecher et al., 1942; Beecher and McCarrell, 1943; Polderman et al., 1943). General circulatory studies involved problems arising from increased pressure in the airway (Beecher et al., 1943). The influence of anaesthesia on the circulation (Bennett et al., 1944) laid the foundation for a long series of wartime studies on "The Physiologic Effects of Wounds", published as a separate volume in the Surgeon-General's history of World War II.

CURRENT WORK

Three fairly distinct areas have gradually emerged from the early work in this laboratory: the metabolic studies are now the principal interest of Dr. John P. Bunker and his associates. The circulatory and hormonal studies are Dr. William R. Brewster jr. and his group's field of interest. The writer, with his colleagues, has for a decade limited most of his investigation to quantitative work on the mental and psychomotor effects of the central nervous system depressants. We have thus prolonged and concentrated interests of a given individual in a given field and yet broad coverage of three widely different areas of importance to the development of anaesthesia.

While we have been fortunate in having the full-time association of physiologists and chemists —their names are recorded in the attached bibliography—it is a firm rule of this laboratory that *all* members of it who are anaesthetists, however great their interest in basic science may be, regularly administer clinical anaesthesia and participate in teaching, both didactic and clinical. We believe that in this way the laboratory's interests and activities enrich our total programme.

METABOLIC EFFECTS OF ANAESTHESIA

For some years this work has been under the direction of Dr. John P. Bunker. Our interest in the metabolic effects of anaesthesia, extending over a considerable period, has led us into a variety of studies. As early as 1940 we were interested in problems of gas exchange during thoracic surgery (Beecher and Murphy, 1940) and were the first to call attention with data to the serious heights to which the carbon dioxide tension could rise when the pleura was open. The fears of Waters, of Crafoord, of ourselves and others of the inadequacy of carbon dioxide elimination using the then current anaesthetic techniques were well founded. Moderate to severe respiratory acidosis was observed during ether anaesthesia with the open chest. Simultaneously, moderate to severe degrees of metabolic acidosis occurred, and this observation further stimulated our interest in the metabolic effects of anaesthesia.

Our initial objective was to determine whether anaesthesia was responsible for the metabolic acidosis or whether the metabolic acidosis was in some way related to the respiratory acidosis. Van Slyke and others, many years previously, had demonstrated severe metabolic and respiratory acidosis in dogs during ether anaesthesia. We have confirmed the occurrence of a metabolic acidosis in the etherized dog, but at the same time have found that in using modern anaesthetic techniques a respiratory acidosis did not occur (Bunker et al., 1951). The next step, a translation of these studies to man, brought out interesting differences. We found with uncomplicated, closed chest anaesthesia that neither a respiratory nor a metabolic acidosis occurs in the normal adult under ether (Beecher et al., 1950). This is true also for cyclopropane as far as a metabolic acidosis is concerned, but under this agent a respiratory acidosis does occur unless the respiration is assisted (Stormont et al., 1942). A metabolic acidosis does not occur under thiopentone anaesthesia (Bunker et al., 1951; Bunker, 1956). On the other hand, infants and small children respond to ether with a metabolic acidosis characterized by high serum lactate and serum pyruvate concentrations (Bunker et al., 1952); and adults themselves under abnormal circumstances (cirrhosis, Cushing syndrome) may develop moderate to severe metabolic acidosis during ether anaesthesia (Bunker et al., 1953).

An attempt has been made to understand the mechanism of these disturbances (Brewster, 1952; Henneman and Bunker, 1957a, b). It was found (Brewster et al., 1952) that a total sympathetic nerve block in the epidural space with dilute procaine, was able to prevent completely the metabolic acidosis, the high serum lactate, serum pyruvate, and in addition, the hyperglycaemia of the etherized dog. The role of reflex action involving the sympathetic nervous system during ether anaesthesia in the dog was thus strongly implicated. Metabolic studies in man, however, suggest that this mechanism may be of little or no importance. Slight but consistent elevations in serum lactate and pyruvate (in addition to the well-known hyperglycaemia) which have been observed during ether and cyclopropane

in the adult might be caused by a reflex outpouring of adrenaline, but changes in serum citrate, alphaketoglutarate, and inorganic phosphorus were found to be in the opposite direction of those produced by adrenaline (Henneman and Bunker, 1957a, b).

Metabolic disturbances may develop during surgery from causes other than the anaesthetic, and these are of considerably greater danger to the patient than any produced by well conducted anaesthesia. Moderate to severe elevations of serum citrate, lactate, and inorganic phosphate during massive blood replacement of surgical haemorrhage have been observed (Bunker et al., 1955). Elevations of citric acid may depress ionized calcium sufficiently to depress cardiac function seriously and possibly sufficiently to prolong clotting (Bunker et al., 1955); however, simultaneous disturbances in all phases of coagulation have been observed and these are of significance in the occasional occurrence of uncontrollable oozing from the surgical field (Bunker et al., 1956, personal communication).

An opportunity to compare the effects of anaesthetic agents on the impaired liver has been of interest. Our original conclusion, based on preoperative and postoperative liver function tests, "that as far as the liver is concerned, anaesthesia is a very small part of the sum of stresses which add up to the total operative insult" (French et al., 1952) has been confirmed by further clinical studies. Venous shunt surgery for the relief of portal hypertension is followed in this hospital by a 25 per cent incidence of postoperative liver failure. During the ten years, up to 1954, studies were made of 140 shunts or attempted shunts, all performed by a single surgeon. The anaesthetics were very evenly spread among ether, cyclopropane, and hypotensive spinal anaesthesia, both as to numbers of patients and severity of pre-operative liver disease. The incidence of postoperative liver failure, as well as the operative mortality, was almost exactly the same for the three different anaesthetics (Ebeling et al., 1956).

The experience we have had in studying metabolic effects of anaesthesia has provided a useful guide for the study of new and controversial techniques as they have been introduced: for example, induced hypotension, hypothermia, and the extracorporeal circulation technique. In carefully chosen patients, hypotensive spinal anaesthesia has produced remarkably little disturbance in acid-base balance, renal, or liver function (Greene et al., 1954). Disturbances in psychomotor function have given cause for alarm, but in a group of patients undergoing surgery of equal magnitude (pelvic exenteration, splenorenal shunt, etc.) under anaesthesia with normal blood pressure, similar, if less frequent, disturbances were observed (Greene et al., 1954).

During uncomplicated hypothermia, in variance with recent reports in the literature, Henneman and Bunker (1957a, b) did not observe metabolic acidosis. When major vessels are occluded, blood transfusions are given, and shivering is allowed, then metabolic acidosis can and does occur. The use of citrated blood is particularly dangerous during hypothermia. Utilization of citrate is depressed as part of the overall slowing of metabolic processes; in addition, as suggested by preliminary observations by Brewster in this laboratory, the hypothermic heart is less able to tolerate a rise in citric acid or a fall in ionized calcium.

Current metabolic studies in this laboratory, under the direction of Dr. John P. Bunker, include: the effect of anaesthesia on liver blood flow using the P^{32} technique of Dobson and Jones (1952) (in collaboration with Dr. George Nardi of the Department of Surgery); the mechanism of antidiuresis during anaesthesia; the immediate physiological disposition of sodium citrate and of calcium chloride, infused independently into experimental subjects and operative patients; disturbances in blood coagulation produced by multiple blood transfusions.

NEUROLOGICAL AND HORMONAL EFFECTS ON THE CIRCULATION

Work in this area is under the direction of Dr. William R. Brewster, jr. We have had a long-standing interest in the physiological response of the organism as a whole to both the anaesthetic agent and the hormonal and ionic changes which accompany the stress associated with anaesthesia and surgery.

Work in this laboratory has demonstrated, as

mentioned, the importance of the role played by the sympathetic nervous system in the haemodynamic and metabolic response of the dog to the administration of di-ethyl ether (Brewster et al., 1952; Brewster and Isaacs, 1953). In the normal animal the positive inotropic effect of adrenaline and noradrenaline, released reflexly from the adrenal medullae and cardiac sympathetic nerve endings, was found capable of antagonizing the direct depressant effect of ether upon the contractility of ventricular heart muscle. The reflex sympathetic response is essential for the optimal maintenance of the contractility of ventricular heart muscle and is essential for maintenance of the cardiac output at the ether concentrations required for all planes of " surgical " anaesthesia. In animals in which the reflex sympathetic response was affected by an epidural preganglionic sympathetic block, the direct myocardial depressant effect of di-ethyl ether was found sufficient to produce critical depression of the contractile force of ventricular heart muscle and cardiac output at arterial ether concentrations of 100–130 mg per cent. It is thus evident that the neuro-endocrine response of the animal, involving the reflex release of adrenaline and noradrenaline from the adrenal medullae and the sympathetic nerve endings in heart muscle, together with an optimum positive inotropic effect of adrenaline and noradrenaline, are factors of primary importance. It was inferred that the clinical safety of ether as an anaesthetic agent was in part dependent upon the neuro-endocrine response of the mammalian organism.

It has been repeatedly demonstrated that all general anaesthetic agents exert a negative inotropic effect directly proportional to their anaesthetic potency and concentration. This fact suggests that the activity of the sympathetic nervous system, through reflexly released adrenaline and noradrenaline, is a factor of primary importance in the maintenance of optimal contractility of heart muscle, and blood flow during the administration of general anaesthetic agents.

Not only is the positive inotropic effect of reflexly released adrenaline and noradrenaline essential in order that the organism tolerate high concentrations of di-ethyl ether, but the same fundamental principle is operative in the presence of elevations in arterial carbon dioxide tensions. In the animal in which a total sympathetic block has been produced either by the epidural injection of a 0.4 per cent procaine solution, or by intravenous ganglionic blocking agents (hexamethonium, pentolinium, or trimetaphan), the maximum carbon dioxide tension that can be tolerated varies between 80–90 mm Hg. When the arterial carbon dioxide tension is elevated above 40 mm Hg in these animals, there is a progressive decrease in contractility and resultant blood flow. As in the case of the intact dog during di-ethyl ether administration an elevation of the arterial carbon dioxide in the normal dog is accompanied by an increased reflex release of adrenaline and noradrenaline. The positive inotropic effects of the latter counteract the direct myocardial depressant effect of carbon dioxide, permitting the animal's heart to tolerate a carbon dioxide tension of at least 240 mm Hg.

The above work points towards a major principle. In the mammal, there are several distinct levels of permissible chemical insult. These levels are low under the circumstances of a total sympathetic block. They may be radically elevated in the presence of normal sympathetic activity.

More complete knowledge of the differential sympatho-adrenal response of the dog, the infant and adult man to such stimuli as di-ethyl ether, increased blood carbon dioxide tension, decreased blood pH, and to other chemoreceptor and baroreceptor stimuli is greatly needed. Recent work reported by Dr. Henry Price (1957) at the University of Pennsylvania has demonstrated that a sympathetic response occurs both in the dog and in adult man during ether administration. He reported an interesting fundamental difference, however, in the character and magnitude of the response. The dog was shown to release adrenaline and noradrenaline both from the adrenal medullae and sympathetic nerve endings. Adult man responded primarily with the release of noradrenaline from sympathetic nerve endings with no appreciable adrenal medullary release of either adrenaline or of noradrenaline.

Implications drawn from the response of the sympathetic nervous system, as described above, suggested the need for a complete study of the

endocrine and ionic variables which might affect the haemodynamic and metabolic response to adrenaline and noradrenaline. The first endocrine interrelationship to be studied was that existing between adrenaline, noradrenaline and the thyroid hormones (Brewster et al., 1956).

The importance of the role of the sympathetic nervous system in relation to the physiological alterations observed during anaesthesia has led to a study of the haemodynamic and metabolic interrelationships in the end-organ activity of adrenaline, noradrenaline, the thyroid hormones and the adrenal cortical steroids. It was found that the physiological alterations of thyrotoxicosis, previously attributed to the direct effects of the thyroid hormones per se, are indeed due to the physiological activity of adrenaline and noradrenaline. This conclusion was reached by demonstrating that thyroid feeding produced the classical haemodynamic and calorigenic effects of hyperthyroidism including significant increase in the heart rate, oxygen consumption, cardiac index, and effective ventricular stroke work.

The metabolic and haemodynamic effects of thyrotoxicosis could be abolished by preventing the reflex release of adrenaline and noradrenaline with a total sympathetic block. Studies done during a one to four-hour period of total sympathetic block demonstrated that there was no significant difference in the oxygen consumption, cardiac indices, heart rates, average right or left auricular mean pressures, ventricular stroke work, and arteriovenous oxygen differences of the thyroid fed dogs as contrasted with the euthyroid group of dogs.

All parameters of activity of l-adrenaline and l-noradrenaline were found to be increased by increased concentrations of the thyroid hormones. The infusion of either l-adrenaline or of l-noradrenaline into thyroid fed dogs with a total sympathetic block resulted in a rise in the oxygen consumption, heart rate, cardiac index, and ventricular stroke work per unit of filling pressure which was significantly greater than that seen during their infusion in a comparable series of euthyroid dogs. Whereas the infusion of l-adrenaline or l-noradrenaline in euthyroid or thyroid fed animals resulted in equivalent inotropic, chronotropic or calorigenic effects, there was a fundamental difference in the glycogenolytic effects of l-adrenaline and of l-noradrenaline, as reflected in the blood and serum concentrations of lactate, pyruvate, and sugar. Whereas the infusion of l-adrenaline consistently resulted in a rise in the serum lactate and pyruvate and blood sugar, the infusion of l-noradrenaline, despite its equal calorigenic effect, produced a fall in the blood and serum concentrations of lactate, pyruvate, and sugar. The normal values of the serum lactate and pyruvate and of blood sugar observed in the thyroid fed animals in the control state suggest that l-noradrenaline is the predominant mediator of the physiological effects of thyrotoxicosis, as far as the activity of the sympathetic nervous system is concerned.

It was concluded that there is a dynamic interrelationship between the thyroid hormones on the one hand and l-adrenaline and l-noradrenaline on the other. The physiological effects of thyrotoxicosis are not the result of the isolated action of the thyroid hormones per se but are due to the physiological effects of l-adrenaline and of l-noradrenaline as augmented by the thyroid hormones. Consideration of the work of others and data from our laboratory indicates that optimal concentrations of the adrenal cortical steroids are essential for the dynamic activity of the hormones of the thyroid and sympathetic nervous system to be manifested.

This work has opened a new pathway for the in vivo and in vitro investigation of the mechanism of action of the thyroid hormones and of l-adrenaline and of l-noradrenaline as they affect transfer and utilization of energy for contraction in heart muscle.

To study the mechanism of action of the above hormones, the effects of temperature upon reaction rates in heart muscle, as indicated by the maximum rates of contraction and relaxation, have been studied (Brewster et al., 1957). Using a 120-ohm bonded strain gauge arch sutured to the right ventricle, the maximum rates of isometric contraction and relaxation in g/second have been observed and related to the contractile force of ventricular muscle in euthyroid and hyperthyroid dogs. The body and heart temperatures of the

above animals have been varied over the temperature 18°C to 43°C. This range spans fairly completely the temperatures at which the dog heart is capable of contracting and doing work.

It was observed that the rate of contraction showed the smallest variation as a function of temperature. The Q10 (temperature coefficient of this rate process over a 10°C temperature range) varied from 1.2 to 1.3. The rate of relaxation showed the greatest variation as a function of temperature. The Q10 of the rate of relaxation varied from 4.3 to 4.6. The spontaneous heart rate (beat/min) and the total oxygen consumption of the animals varied as a function of temperature with Q10 coefficients varying from 2.10 to 2.70.

The Q10 of the rate of contraction indicates this phase of heart muscle activity to be a physical process not involving chemical bond energy or electron transfer. It is consistent with the view that contraction is the result of an ionic interaction between actin and myosin in which these molecules lose their charges and form the insoluble precipitate, actomyosin.

The Q10 of the rate of relaxation indicates this phase of activity in heart muscle as a phase requiring active transfer of chemical bond or quantum energy to return the proteins, actin and myosin, to their extended, dissociated, and charged state. The rate of relaxation can be regarded as the rate of phosphate bond energy transfer. This is consistent with the view that in terms of the internal energy of the system, the contracted state is a low energy state while the extended or relaxed state is the charged high energy state. Contraction involves the decrease in free energy and the incidental performance of work. Relaxation is an active chemical process increasing the internal energy of the contractile protein system.

Focusing upon the rate of relaxation as a rate process indicating energy transfer, it has been found that adrenaline and noradrenaline, when injected in physiological concentrations, primarily increase the rate of relaxation of heart muscle. It is postulated that the increase in contractile force of heart muscle produced by adrenaline and noradrenaline may be due to their augmentation, directly or indirectly, of quantum energy transfer to the contractile proteins. (This is consistent with the high oxidation reduction potential of adrenaline.) The thyroid hormones have been found to have no effect upon the rate of relaxation or upon energy transfer in the absence of adrenaline and noradrenaline. Their activity in the presence of the sympatho-adrenal hormones can be explained by considering thyroxine and tri-iodothyronine, both amino acids, active only when incorporated into the polypetides actin and myosin. In these proteins, their heavy iodine ions can serve as localizers of electron charge density. As such, they would increase total coulomb repulsive forces between charged points in the protein molecule. This factor would both increase the rate of dissociation of actin and myosin and increase the internal energy of the dissociated system.

It has also been observed that when the "contractility" of heart muscle is depressed by anoxia, anaesthetic agents, or by increased blood carbon dioxide tension, the primary characteristic of depression is a parallel decrease in contractile force and rate of relaxation. This has raised the possibility, to be thoroughly investigated, that the primary effect of an anaesthetic agent is to block the transfer of energy from high energy phosphate bonds to the contractile proteins.

This work is being continued and extended by Dr. Brewster.

SUBJECTIVE RESPONSES

For a decade my own work has been largely directed to this area. It is probable that pain is the first problem the physician was asked to treat. It is also probable that, because of its antiquity, it has gathered about it more folk lore than any other medical problem. My own special interest in investigation has been to try to cut through the false problems to the real ones by the application of quantitative methods in the elusive field of subjective responses, in short to measure the effects of drugs on pain. This problem is broader than pain alone and I have long considered that this work on pain is a prototype for the quantitative study of subjective responses in general.

The material we use is largely *severe* postoperative wound pain. An important question is, how representative are the conclusions one can draw from this material, how broadly can one's conclusions be applied to pain problems in general?

A reassuring answer is shown by the remarkably close checks between our findings as compared with those of Houde and Wallenstein at the Sloan Kettering Laboratory. They studied chiefly pain arising from metastatic cancer. The agreement of the two independent laboratories using different pain sources was as exact as the agreement from time to time within a given laboratory for pain from one source (Beecher, 1957).

The methods we use and the controls involved have been described (Denton and Beecher, 1949; Keats et al., 1950; Beecher, 1952a, b, 1953, 1957) in detail elsewhere. Briefly, the procedure is to take 25 or more individuals in severe postoperative pain, set up standards of partial and complete relief, administer drugs in a random fashion, using the "double unknowns" technique wherein neither the subject nor the observer is aware of what was used, insert placebos also as unknowns, use "correlated" or "cross-over" material (all subjects receive all agents), and validate mathematically supposed differences. When these essential controls are employed one can work within a 10 per cent error. The accuracy involved in dealing with the effects of drugs on subjective responses is as great as when one deals with objective measurements of therapeutic effects in man.

One reason why this work has seemed particularly interesting is that the results are useful in two areas, the theoretical and the practical. For example, the rapid flattening of the dose-effect curve, the rapid achievement of a ceiling effect, on increasing the dose of morphine, say, indicates that the optimal dose of morphine per 70 kg of body weight is 10 mg (Lasagna and Beecher, 1954a), for increase of the dose to 15 mg adds little to the pain relief but does seriously increase the side effects to a point approaching undesirability. This brings to the fore a problem of definition wherein we must recognize that to appraise pain relieving agents two scales of values must be taken into account: (*a*) side effects per mg and (*b*) pain relief achieved per mg; classically, this would be called potency; to use this definition of potency alone would be most confusing, for example, one would say that pethidine was a weak agent, only one-fifth as strong as morphine, and this would be ridiculous, for in optimal dose pethidine is as potent as morphine. A somewhat surprising finding on the quantitative techniques mentioned is that 50 mg pethidine equals 10 mg morphine in pain-relieving power (Lasagna and Beecher, 1954b).

It must be made clear that while it is easy to speak of side effects, it is difficult to be certain that one evaluates them properly. There are a number of reasons why pain must usually be studied as it arises in disease, rather than to depend on pain experimentally produced, if one's purpose is the appraisal of analgesic agents. These matters have been discussed in a long review (Beecher, 1957). The difficulty is that when one employs, as is usual for this purpose, pain arising in disease, the disease itself often carries with it symptoms like those produced also by the agents in question—nausea, for example—and it is difficult or impossible to get at the exact truth. On the other hand, the use of normal subjects is not entirely satisfactory either, for it is not possible to be sure that morphine would not produce less nausea in the individual who was distracted by the pain and worry of his disease. Clearly, conclusions in this area must be guarded.

On the surface of the matter, the subject of side effects is rather prosaic, even dull; but I hope I can show that there is something exciting to be found here too. The principal physical side effects of narcotics, respiratory depression, vomiting, constipation, are well known and easily measured. On the mental and physical side combined there is addiction. (This is far outside my field of competence and will not be dealt with here.) Of the "mental" or subjective side effects there is nausea, and we have worked out techniques for measuring this (Knapp and Beecher, 1956); then there is "mental clouding" or confusion for which we have recently been obliged largely to develop our own psychological techniques in quantitative terms (Smith et al., 1957). Heretofore the confusion "mental clouding" produced by drugs has not been expressed quantitatively. The techniques we have evolved for measurement of mental clouding are broadly applicable to many problems, for example, to study the enormous new field of the so-called tranquilizers.

To return to the question of other practical advances, there are the data on comparative doses

of common analgesic agents, referred to in the case of pethidine. There is the demonstration that codeine, even in 60 mg dose or larger, administered parenterally, never achieves the pain relieving power of 10 mg morphine, but codeine does have, at 60 mg, side effects practically identical with those of 10 mg morphine, except for addiction liability (Lasagna and Beecher, 1954b). There is the recent finding (Gravenstein et al., 1956) that dihydrocodeine in 30 mg dose is a very powerful analgesic, although not quite so powerful as morphine, but, remarkably, it has no more side effects than a placebo, in the 30 mg dose. This is the first time a really powerful analgesic has been found that is not associated with severe depression of the respiration, frequent nausea and mental clouding. It marks a milestone in the long road to improvement of narcotic agents.

On the " basic science " side the mechanism of action and the site of action of drugs have long been of interest and some progress has been made in getting at these matters. As long ago as 1895, Strong, stimulated by a book written by Marshall the year before, postulated that suffering consists of two parts, the original sensation and the psychological reaction to that sensation. The concept is probably a very old one, for Voltaire commented in 1768 that there is no such thing as a sensation without a thought about that sensation. As we pass through life, there is a conditioning of familiar sensations. We have been able to support Strong's hypothesis with data which indicate that one site (and probably the principal one) for the action of drugs which modify subjective responses is the psychological reaction or processing component.

In the first place, there is reason to doubt that analgesic agents have power to modify the " original sensation ". Fifteen groups have now failed to confirm the reports of Hardy et al. (1952) and others who use pain of experimental origin, and who have failed to confirm that the pain threshold is dependably responsive to the action of such agents (Beecher 1956a, 1957). This is negative evidence. It should be explained that the experimentalists such as Hardy et al. (1952) hold that the pain threshold measures the " original sensation ".

On the positive side there is much evidence that factors which could not conceivably affect the pain apparatus in a drug-like way yet can be of dominating importance, presumably through altering the psychological reaction component. For example, there is the powerful placebo (Beecher, 1955b). We have been able to show in seven of our own studies and in eight from other laboratories, involving over a thousand subjects, that placebos have an average effectiveness of 35 per cent $\pm$ 2.2. When it is recalled that even a large dose of morphine, 15 mg, satisfactorily relieves (as defined) only 75 per cent of subjects in severe pain, it can be seen that the placebo accounts for nearly half of the possible drug effectiveness. It has been possible to present evidence when the stress is severe that the effectiveness of placebos is greater than this. Thus it was shown (Beecher, 1956b) when the pain is most severe that placebos account for 77 per cent of the effectiveness of the analgesic (10 mg morphine).

In a still different type of study further evidence was obtained for the importance of the reaction component. Wounded soldiers (Beecher, 1946) who are clear mentally, not in shock and who have had no analgesics at all in many cases and in no case within 4 hours, have enough pain to want anything done about it in only 25 per cent of the cases. Civilians having much less tissue trauma as a result of surgical procedures than the soldiers, have enough pain to want pain relief in over 80 per cent of the cases. This cannot be explained on the basis of familiarity with narcotic agents on the part of the civilians, for the same high percentage held whether the surgery was necessary because of long illness, as with cup arthroplasty, or whether it was required by fresh fracture of bone. The explanation appears to lie in the significance of the wounds: the soldiers, most of whom were studied on the Anzio beachhead where imminent death seemed likely, considered their wounds to be a ticket home. The war was over for them. They were not unhappy with their lot. To the average civilian the necessity for surgery is a calamity. The significance of the wound seems to determine the suffering experienced. These examples provide

evidence that factors which affect the psychic reaction component can dominate the pain experience (Beecher, 1956c) and thus provide evidence for the first time that Strong's 62-year-old hypothesis is correct.

The techniques which have been described in some detail have been applied to other problems, especially to a quantitative study of changes in mood produced by drugs (Lasagna et al., 1955; von Felsinger et al., 1955). They have been applied to cough (Gravenstein et al., 1954). They are being applied as already mentioned, to measuring the "mental clouding" produced by narcotic drugs (Smith et al., 1957) and to a study of itch (Macris and Beecher, 1957).

CONCLUSION

In the 21 years of existence of the Anaesthesia Laboratory some 200 papers have been published from it. No attempt has been made to review all of this work, but, rather, typical examples have been presented in order to give some idea of the kinds of problems we have found of interest. We believe that useful contributions to knowledge have been made in the course of this work: but however that may be, we are firmly of the opinion that a direct consequence of these painstaking enquiries is better teaching, with the inculcation of a critical, but not destructively critical, attitude on the part of those we have trained. We believe that the development of such an attitude is essential for the long range and sound development of our specialty.

Experimentation in animals has given rise in the past to very great discoveries; it will in the future. Without in the least minimizing the importance of animal experimentation now or in the future, it is fair to point out that there is rightly an increasing interest in human physiology and in human pharmacology. It is clear when one studies the effects of the central nervous system depressants, that man has become the medium for much of such work.

In the studies described in the preceding pages new questions have been asked; some have been answered; but only the surface of an area has been scratched which can have great importance in the development of medicine. It needs long range planning. It needs long range support.

ACKNOWLEDGMENTS

No account of the Anaesthesia Laboratory would be complete without acknowledgment of the long-standing and generous support of Mr. Edward Mallinckrodt and the Mallinckrodt Company; of the United States Public Health Service; of the Medical Research and Development Board of the Army; of the Air Force and of the National Research Council through its Committee on Drug Addiction and Narcotics from funds contributed by a group of pharmaceutical manufacturers. These have been our principal sources of support through the years. They are acknowledged with gratitude.

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CORRESPONDENCE

IRREVERSIBLE CURARIZATION

Sir,—May I express my disagreement with Dr. Burchell. At the conclusion of his only too topical article on irreversible curarization (*Brit. J. Anaesth.*, 1957, **29**, 127) he recommends that "until the aetiology has definitely been established, all routine drugs must be tried".

For several years I have been teaching that this is exactly what one must not do. Apnoea persisting at the end of operation may be due to such a number of different causes that there can be no specific treatment. Any symptomatic treatment may well be ineffectual and can often be dangerous. I am convinced that in many of these cases which end fatally, the cause of death is not the apnoea but the treatment directed at the patient in impatient, misguided attempts to restart spontaneous respiration—dangerously large doses of neostigmine, powerful medullary stimulants such as nikethamide, vigorous overventilation with an absorber in situ or alternately leaving the patient apnoeic for a minute or two—all measures calculated to impose a considerable strain on the fittest of subjects.

A frequent history is that at the end of operation "the patient was in a reasonably good condition and only began to go downhill subsequently when restorative measures were applied". Dr. Burchell reported that his own patient was in "excellent" condition. I am convinced that the only safe way to treat these cases is to be patient, to maintain normal pulmonary ventilation, preferably with a mixture of about 5 litres nitrous oxide and 3 litres of oxygen without an absorber, and to direct all one's efforts at diagnosing and then removing the particular underlying cause. Until the latter has been established, patience must be the watchword and drugs must be withheld. Apnoea is not of itself lethal, and correctly treated apnoeic patients can survive almost indefinitely. Correct treatment however, does not include the hopeful, indiscriminate administration of a variety of potent drugs.

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Brit. J. Anaesth. (1957), **29**, 274

THE ROLE OF THE ANAESTHETIST IN THE ASSESSMENT AND TREATMENT OF INJURY AT THE ACUTE STAGE

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THE anaesthetist may be involved directly in the immediate care of seriously injured patients in resuscitation, anaesthesia for urgent surgery, or both. In any case he must be able to assess the clinical state of the injured patient in conjunction with the surgical team.

The most important recent advance in the care of patients with major injuries has been the recognition of the extent of blood loss associated with injury and the benefit derived from its replacement by transfusion of stored blood. Studies of the extent of haemorrhage following trauma have resulted primarily from the development of techniques for determining blood volume, either from the Evans Blue plasma volume and haematocrit, or from the cell volume using erythrocytes labelled with radioactive phosphorus (P^{32}) or chromium (Cr^{51}) (Davies, 1956).

Corroborative evidence of the extent of blood loss can be derived from routine follow-up haemoglobin studies (Topley and Clarke, 1956). Blood loss during surgery can be estimated by swab weighing or measurement of blood sucked out of the abdominal cavity or aspirated from the chest.

Indirect evidence of blood loss into the tissues can be obtained by measurement of limb swelling at the acute phase (Clarke, Topley and Flear, 1955). Correlation of the appearance of wounds or closed injuries with blood volume studies can facilitate the assessment of blood loss from the nature of the injuries (Clarke and Fisher, 1956). Experience with swab weighing in the operating theatre can train anaesthetists to make their own visual estimates with a useful degree of accuracy. Clinical observation of patients on whom blood volume studies have been carried out can assist in the assessment of local or general signs as evidence of the presence and extent of haemorrhage or oligaemia.

Our investigations and experience have shown that the general conclusions enunciated by Grant and Reeve (1951) following their investigations during World War II are fully relevant to an important proportion of civilian injuries. They stress the frequency and extent of whole blood loss in battle casualties, the need for larger blood transfusions, and the relative unreliability of the blood pressure and pulse rate as quantitative indicators of changes in blood volume.

We have emphasized the contribution of blood loss into the tissues in association with closed injuries, especially fractures, and have developed the thesis of Grant and Reeve that the nature and extent of injury frequently constitutes the best guide to the extent of blood loss.

BLOOD LOSS FROM CLOSED INJURIES

Blood loss from closed fractures of the limbs can be crudely assessed from the volume of primary swelling. The likelihood of continued bleeding into the tissues can be based firstly on direct observation, secondly on an understanding of the mechanism of injury and its anatomical extent, especially in relation to the probability of muscle damage or vascular injury. Many straightforward closed fractures of the ankle, os calcis, tibia and fibula, forearm, elbow or shoulder can be associated with the loss of one pint ($\frac{1}{2}$ litre) of blood into the extremity. This in itself need cause no anxiety and obviously does not need replacing, but a number of such injuries may add up to a significant loss of blood. More severe fractures of the tibia and fibula and many closed fractures of the femur are associated with a primary blood loss of the order of 2–4 pints (1–2 litres). Severe fractures of the shaft of femur with major swelling may lead to much greater loss of blood. On several occasions we have seen patients who

have lost half their total blood volume into the tissues of an injured thigh. Recent studies have shown that wide extravasation of blood can be associated with fractures of the ribs, and that even without a major haemothorax moderate chest injuries can be associated with a blood loss of 1–1½ litres, without this being obvious from the surface. Closed fractures of the pelvis, particularly when associated with visceral injuries, can cause the loss of very much larger quantities of blood and continued massive transfusion may be necessary for resuscitation, particularly where major surgery is required for the repair of a ruptured urethra or damaged rectum.

BLOOD LOSS FROM OPEN INJURIES

Blood loss from open wounds which occurs before admission to hospital is difficult to assess. In battle casualties Grant and Reeve (1951) have suggested that a crude guide to the total blood loss in limb injuries can be based on the extent of tissue damage, roughly assessed in terms of the volume of the human fist. This guide is in our opinion of only partial value in the majority of civilian injuries. Small lacerations may divide medium sized blood vessels with haemorrhage out of proportion to the size of the wound. Many patients with major lacerations of the forearm and hand can lose 2–4 pints (1–2 litres) before admission to hospital. They can continue to bleed through dressings whilst awaiting operation. In the ordinary run of open fractures the majority of which are " compound from within ", we have found that the extent of blood loss to the outside is frequently of the same order as the extent of bleeding into the tissues, so that open fractures tend to cause the loss of about twice as much blood as do similar fractures without skin penetration. Some major injuries of a crushing type are associated with early obliteration of the vessels and relatively little blood is lost. On the other hand, patients with major amputations, particularly through the thigh, lose more blood than is usually anticipated and continue to lose blood into tissues around the amputation stump. They frequently require not only large primary transfusions but repeated transfusions to maintain a normal quota of red cells.

We have presented elsewhere (Clarke, Topley, and Flear, 1955; Clarke and Fisher, 1956) a number of case histories with photographs and detailed blood volume studies to illustrate the general conclusions here presented.

Important additional evidence on the extent of blood loss in certain types of battle casualties was obtained by American research workers during the Korean War (Howard, 1956; Prentice et al., 1954). They found evidence of disappearance of red cells even greater than was the general experience in World War II, and reached the conclusion that this red cell loss was primarily due to haemorrhage, although some of the disappearance of red cells could be explained by their use of uncrossmatched Group O blood and a degree of haemolysis that has not been encountered in our studies.

BLOOD LOSS AND CLINICAL SIGNS OF " SHOCK " (Clarke, 1956)

Injured patients presenting the classical picture of established " haemorrhagic shock " with pale cold extremities, a systolic pressure below 70 mm of mercury, a rapid pulse rate and obvious bleeding have probably lost at least half their total blood volume by haemorrhage. When surgery is needed they will almost certainly require a transfusion of the order of their total blood volume (4–7 litres) and occasionally much more. Patients with less obvious haemorrhage but with diagnosable closed injuries presenting the same clinical picture must be regarded as suffering from haemorrhage of the same extent. They require the same quantities of blood replacement.

Patients with trivial injuries can for a very short period of time present a somewhat similar picture. There is certainly a form of purely neurogenic shock that needs to be differentiated from the effects of haemorrhage. But even this condition is predisposed by any pre-existent loss of blood. In the absence of continuing major irritation to the nervous system, this type of neurogenic " shock " will respond very rapidly if the patient is kept flat. In the presence of evidence of major injury it is very dangerous to assume that a patient reaching hospital in a state of apparent circulatory collapse is suffering from a purely neurogenic response with no underlying component of oligaemia.

Blood volume studies have now established that patients with 15–30 per cent of whole blood loss may show no evidence of circulatory upset. More frequently such patients are pale and their extremities take longer to warm up than those of an individual not suffering from haemorrhage. A proportion of patients with total blood loss of 25 per cent will be found to have a raised blood pressure, the " hypertensive phase " described by Grant and Reeve. This is sometimes associated with pain and anxiety. It appears to be more likely to develop in the presence of severe tension in an injured part even if this is not associated with pain. The raised blood pressure does not necessarily respond to morphine, usually disappears under anaesthesia, but may recur subsequently unless the blood volume is restored to normal. The presence of a high blood pressure is no indication for witholding transfusion from a patient known to be oligaemic. It is particularly important that this should not be overlooked in children because the hypertensive phase may be followed by sudden fatal collapse.

When patients are seen soon after injury ($\frac{1}{2}$–2 hours), a low blood pressure—less than 100 mm of mercury in a young man—or a low pulse pressure—20 mm of mercury—frequently indicates blood loss of 25 per cent or over.

The pulse rate may be of more significance than we had previously supposed and the quality of the pulse may give an important indication of deterioration. On the other hand, it is probable that a rise in pulse rate associated with moderate haemorrhage may be due to some other factor—developing pneumothorax or peritoneal irritation. Clinical evidence of the state of the circulation is useful but frequently gives a misleading picture of the degree of oligaemia, and impressions derived from such evidence should be ignored when the nature of the injuries clearly indicates a greater degree of haemorrhage.

SIGNIFICANCE OF BLOOD LOSS

So far we have discussed oligaemia in terms of whole blood loss. There is now an overwhelming body of evidence that in the majority of non-thermal injuries oligaemia is in fact due to whole blood loss. It is only in burns, the occasional crushing injury and in the presence of established peritonitis, that there is a loss of plasma-like fluid from the circulation unassociated with loss of red cells. It is probable that in many closed injuries there may even be reabsorption of fluid and electrolytes from the site of haemorrhage into the injured tissues even while further haemorrhage is still taking place, so that red cells are lost to a greater extent than the fluid component of blood. It is generally agreed that in severe haemorrhage transfusion of whole blood is the treatment of choice. When there is a shortage of whole blood, plasma and plasma substitutes may play a limited role in maintaining the circulation for a short time. With an adequate transfusion service there is little evidence that they are anything but a second or third rate substitute for whole blood.

Minor blood loss need not always be replaced in toto. Healthy subjects can lose $\frac{1}{2}$–$1\frac{1}{2}$ litres of blood and even more without any immediate danger to life. If they do not need to be moved and do not require surgical treatment, the loss of such quantities of blood can be left to take care of itself. In patients requiring surgery, in the elderly and in the very young, and in all patients who are in any way systematically sick, even the loss of 1–3 pints of blood may decisively contribute to the risk to life. Many patients with fractures of the shaft of the femur have collapsed following transport without splintage, turning, anaesthesia, or surgery. A patient who has lost 1–2 pints of blood from closed fractures may collapse dangerously from quite minor bleeding lacerations unless the bleeding is promptly arrested. Many of the problems associated with anaesthesia in the injured patient are facilitated by recognition of the extent of blood lost and its accurate and timely replacement.

The role of transfusion, moreover, is not confined to the period of primary resuscitation and anaesthesia. Continued postoperative bleeding, especially from amputations and major orthopaedic interventions, is usually underestimated and may require continued transfusion.

On the other hand, moderate bleeding is followed by haemodilution and the blood volume may be restored by a transfusion which is inadequate to replace the lost red cells. In the past it

has been recognized that transfusion for anaemia plays a vital part in the treatment of established wound infections. The prevention of post-traumatic anaemia by full blood replacement appears to contribute to the prevention of infection and the better healing of wounds, especially where the circulation has been interrupted by trauma. The rapid correction of oligaemia certainly plays a part in the prevention of traumatic anuria, and there is evidence to imply that prolonged uncompensated oligaemia predisposes to liver failure, and to cerebral or coronary thrombosis in patients with degenerative conditions of the vascular tree. Clinical observations (Clarke, 1952) suggest that transfusion sufficient to maintain the red cell volume leads to quicker and smoother convalescence. Flear and Clarke (1955) have shown that this improved convalescence is associated with alterations in the metabolic and electrolyte response. Water and sodium retention are certainly reduced by adequate transfusion.

Topley and Fisher (1956), Flear (1956) and others have suggested that a variety of complications which may follow surgery or trauma are favourably influenced in proportion to the adequacy of transfusion. There is probably no substitute for red cells lost by haemorrhage except whole blood transfusion and the evidence is increasing that stored blood is as effective for cell replacement as fresh blood. Those responsible for transfusion must consider not only the immediate effects of oligaemia but the long term events which may be adversely affected by a shortage of red cells. This is an additional reason for a cautious attitude to the use of plasma or plasma substitutes when whole blood has been lost.

TRANSFUSION RISKS

The advantages of replacing lost red cells by transfusion must obviously be weighed in the balance against the risks involved, and perhaps to a lesser extent against the organization required.

The methods of assessing blood loss, as detailed previously, frequently make it possible to estimate blood requirements in time to allow for accurate grouping and full crossmatching. The overwhelming majority of transfusions for acute injury at the Birmingham Accident Hospital have been of type-specific blood. Patients with severe blood loss cannot wait, but the majority with moderate injuries—not obviously bleeding rapidly—can wait at least half an hour for grouping and emergency crossmatching, whilst many can wait two hours for full crossmatching. The primary grouping must include the rhesus factors in addition to the ABO group.

During the past eight years we have lost one patient from an incompatible transfusion. With an efficient organization and careful checking at all levels, the danger to life from transfusion itself need be no greater than the risk of expert anaesthesia for a minor operation on a fit patient. The greater risk is of transfusing too rapidly at the wrong time, but even this is very much less today than the risks involved in transfusing too slowly and too late.

In the presence of clear evidence of bleeding, the earlier a patient is seen the more rapidly can blood loss be safely replaced. The greater the extent of blood loss the more is speedy replacement urgently required. Patients with a blood loss of 40–50 per cent of their total blood volume, particularly when this is associated with severe injury, should be transfused as rapidly as possible. The intravenous route is usually as efficient as intra-arterial transfusion. With the aid of pressure and a large bore Guest cannula a bottle of blood can be transfused into a single vein in about four minutes. Occasionally it is necessary to set up several transfusions at once.

With less severe haemorrhage the transfusion can be kept going as a continuous stream until it is estimated that the blood volume has been restored to normal. It can then be adjusted to a fast drip and further timing based on observation of further bleeding or on the patient's general condition. In my opinion the colour of the toes frequently provides a very useful guide to full blood replacement. For moderately severe injuries I aim to replace blood loss by the end of the anaesthetic administration and this should leave the patient not only with a warm and pink nose and ears but with warm pink toes. Further transfusion should be discussed with the surgeon concerned in relation to all the factors mentioned previously.

When there is delay in the patient's reaching hospital so that haemodilution is likely to have taken place, transfusion should be more cautious

except in a condition of advanced "shock". In old people and particularly in those where there is evidence of disturbance of pulmonary or cardiac function, greater care is needed. On the other hand, such patients stand blood loss and under-transfusion just as badly as a transfusion which is excessive in quantity or administered too rapidly.

With added accuracy in the assessment of blood loss it is possible to ensure that the majority of patients with moderate injuries come to the operating theatre not only with a normal blood pressure, pulse rate, skin temperature and colour, but with a blood volume which is nearly normal. Under such conditions definitive surgery can be carried out without undue haste and with a high degree of safety. This is of great importance in trauma because the early hours following injury frequently provide the only opportunity for adequate repair of injured tissues and adequate wound surgery to prevent infection.

When there is evidence that progressive bleeding particularly into the abdominal cavity, is taking place faster than can be replaced by transfusion, surgery becomes an essential part of the resuscitation process and must be carried out whilst the patient is still improving; transfusion must be continued throughout.

ANCILLARY METHODS OF TREATMENT

Our advancing knowledge of the role of transfusion is associated with clearer conceptions of the physiological disturbances associated with the response to blood loss in trauma. We no longer attempt to treat the coldness of the patient's extremities by artificial heating. A patient with a minor injury may be comforted with a blanket but there is never any indication for the use of hot water bottles or hot cradles. In warm weather the injured patient does not require more than a single blanket and even this is usually unnecessary during the course of anaesthesia.

It is now fully recognized that such drugs as morphine and pethidine should not be injected subcutaneously to a patient with an obvious deficiency of the peripheral circulation. These drugs are beneficial when given for pain or extreme restlessness and anxiety. When necessary in acute "shock" they should be given intravenously and in small doses, repeated as indicated by the response of the patient.

Position is important. The patient in a state of severe collapse can with advantage be nursed with the head of the table tilted down. Most other patients should be nursed flat except when chest injuries make it difficult for them to breathe properly in this position.

The need for oxygen is less than the need to clear the airway, particularly in the presence of bleeding from a fractured skull or jaw or lacerations around the mouth. Tracheal or bronchial suction or intubation may be required under such conditions; assisted respiration may be useful, and many patients with head injuries, cut throats and paradoxical respiration with a loose segment of the chest wall, benefit from early tracheotomy carried out under local anaesthesia. A severely injured patient may be upset by any movement, although this may be necessary for examination and radiological investigation. All interference is likely to be safer if it can be delayed until the blood volume has been restored to something like normal.

Since many of the above procedures are closely related to the normal activities of the trained anaesthetist, and particularly as the anaesthetist will have a major responsibility during the anaesthetic period, I am convinced that wherever possible a member of the anaesthetic staff should be available as part of the resuscitation team at the earliest possible moment following the admission to hospital of a severely injured patient. He will not only play an invaluable part in the pre-operative handling of the patient but will have the opportunity to form independent assessments of the need for blood and of the indications for and timing of transfusion.

COOLING AND THE USE OF CHLORPROMAZINE

During the last few years there has been a great amount of discussion, research and clinical observation concerned with cooling, and with attempts to alter the general state of reactivity of sick and injured patients with chlorpromazine and allied drugs, the "lytic cocktail" in various forms, with or without artificial cooling.

In cardiac surgery it would appear that cooling can make a decisive contribution to the safety of

direct surgical intervention, particularly in association with methods of maintaining the circulation to essential organs by mechanical means. The early suggestion (Laborit, 1952) that the treatment of the severely injured could be transformed has not yet been substantiated. There is a widespread clinical impression that chlorpromazine is a useful adjunct to premedication and anaesthesia. There are reports of individual patients who appear to have benefited from cooling and chlorpromazine, and of other new drugs which have contributed to the possibility of safe prolonged states of sedation.

The general conception of altering the whole nature of the individual response to trauma, so that excessive reactions are modified and the general metabolic needs decreased, is of profound interest from a long term point of view, but in my opinion we need to know much more about the physiological disturbances present during all phases of the illness of trauma before we can assess the practicability of this method of approach. From the purely empirical point of view we need very detailed observations on all patients receiving treatment of this kind.

It is important, moreover, that the complex difficulties, which underlie the making of a full diagnosis in severe injuries, should not be further complicated by drugs whose detailed actions have not yet been fully evaluated, without overwhelming evidence of the beneficial character of their clinical action.

A number of other observers have advocated the use of noradrenaline in states of "shock". This is likely to be even more dangerous as a general approach. There may be individual patients who can benefit from the "lytic cocktail" and others who might benefit from noradrenaline. The majority of patients reported in the literature could well have recovered with transfusion alone in adequate doses at the right time. The whole subject still requires much careful clinical and research study.

Meanwhile, no illusion that "shock" is a single simple entity or that it can respond to a specific drug, should distract from the careful assessment of blood loss and the continued evaluation of its quantitative replacement.

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CHOICE OF ANAESTHETIC*

BY

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CHOICE of anaesthetic is too big and too difficult a subject for me to deal with comprehensively. I have perhaps rather foolishly chosen to write about one or two aspects of the problem that interest me, and although there is no great originality in what I have to say, I hope that I may be able to use my folly as a stalking-horse, under the presentation of which I can shoot, if not my wit, at least a few provocative darts.

Benjamin Ward Richardson wrote of John Snow that throughout his life he sought for a perfect drug "which, having the physical properties and practicability of chloroform, should, in its physiological effects, resemble ether in not producing by any accident of administration, paralysis of the heart". Since that time, pharmacology has become a more exact science, and choice of anaesthetic a more difficult matter. In the early days of anaesthesia an agent was chosen as the sole drug to be used in a particular case; to decide upon ether, for example, was to accept as inevitable the dangers and inconveniences resulting from the production of suitable operating conditions by the use of ether alone. The idea of using combinations of drugs arose much later, and although local and spinal methods had shown that analgesia and relaxation are not inseparable from narcosis, and the production of narcosis without relaxation must have been practised from the beginning with nitrous oxide, it was not until much later still that a clear separation of the component parts of anaesthesia was formulated. Our search today is for a perfect combination of easily administered and completely predictable drugs, each with a specific pharmacological action and no side effects. A complete range of such ideal drugs is not yet available, of course, but a great deal of contemporary anaesthetic practice is based on the intelligent combination of what each anaesthetist believes to be the most suitable agents for specific purposes. This aspect of the problem receives constant attention, and it would be superfluous to enumerate here the advantages and disadvantages of every drug and technique, or to catalogue all the pathological states that may be found in patients undergoing various operations. However, a study of the literature dealing with anaesthesia for a particular operation or a particular class of patient brings us face to face with the most fundamental difficulties. There is no single answer to any anaesthetic problem; the literature is full of opinions, but, although these may each have a sound basis, they are often at variance, and sometimes contradictory. Medicine, as Proust said, is not an exact science, and just as each man's world is an inference made from what his senses have perceived, so each anaesthetist's opinion of a technique is a conclusion drawn from what he has known it to do.

The purpose of the literature is to present these conclusions for the general good, and it is of vital importance to investigate the validity of this procedure, since it is to all intents and purposes the only source of information available for study of the problem of choice of anaesthetic. Anaesthetists do not as a rule subdue their victims, as bullfighters do, before a vast audience; and yet, privately, anaesthesia has something of the same sort of ritual about it, and a great deal of the same element of individuality. There are conventions to be observed, within the superficial sameness of which each exponent has his particular method of approach, and even the same approach will not always have the same effect. The tactics are modified to suit the constant change of circumstances. What is to be done is laid down in the

* Essay submitted for the Registrars' Prize for 1956 by the Liverpool Society of Anaesthetists.

books; the way it is done will perhaps separate life from death. But all this is lost without an audience; alone in their separate anaesthetic rooms, anaesthetists suffer in the lack of professional critics a deficiency which the literature must make up as best it can. Unfortunately the ability, which Guedel showed so brilliantly, to bring to the reader's mind a living picture of events is rare, and in this age of controlled experiments and clinical trials it is an ability not much exhibited even by those medical writers who may possess it. The record card, being more reliable than mere clinical impression and memory, forms the basis of the series, and the series becomes the literature, but the realities of anaesthesia as an art comprise more than can ever be found in print. A record card is no more an anaesthetic than a musical score is a performance; no amount of scrutiny of the printed page will enable us to imagine the sound of a sonata under the hands of a particular pianist, and it would be as fatuous to suppose that a record card can give the answer to a difficult anaesthetic problem as to suppose that the buying of Debussy's " Preludes " is all that is needed in order to play them like Gieseking.

Perhaps not many anaesthetists would seriously think of turning to a single record card for guidance in the matter of choice of anaesthetic, but a great many anaesthetists, every day, seek guidance from the literature, and, as we have seen, the literature consists largely of record cards, grouped and statistically analyzed. Now there are many problems, such as the evaluation of new drugs, for example, for which statistics are invaluable, but when an attempt is made to apply statistical conclusions to individual cases, great difficulties are encountered. The statistical method is essentially inductive; if, in a sufficiently large series of cases, the incidence of a given event is x per cent, it is argued that its incidence will always be x per cent, however much larger the series may become. There is some justification for this belief, in some cases, but a clear distinction must be made between this kind of probability and a different kind, that might be called " likelihood ", which arises in clinical practice. It may be shown, perhaps, in a large series of cases, that the incidence of a certain complication under cyclopropane is 20 per cent, but what does this tell me about a particular patient I am to anaesthetize? In one sense it may be true that the mathematical probability of his developing the complication is 20 per cent, he has a one-in-five chance; but he cannot develop one-fifth of a complication, the incidence in his case must be either 0 per cent or 100 per cent, which bears no resemblance to the state of affairs in the series as a whole, and is just a way of saying that without further evidence we cannot know whether he is one of the people who will develop this complication or not. However, in another sense, the " likelihood " of his developing the complication may depend, to the best of our belief, on certain definite things. The " likelihood " of arrhythmia, for example, depends on the patient's age and physical type, the depth and duration of anaesthesia, and the anaesthetist's skill in using cyclopropane and his knowledge of the dangers of hypoventilation and carbon dioxide accumulation. From a consideration of these various factors it may be possible for me to form a fairly concrete impression of whether or not this particular patient is likely to develop this particular complication, and I may even be able to estimate against my own mental yardstick the degree of " likelihood ". Although this " likelihood " is not an accurately measurable probability, I have more chance of selecting a successful technique by going through a series of mental processes of this kind in respect of different complications, than I have if I rely blindly on statistics, for these mental processes, in their most highly developed and subconscious form, are what we call judgment and experience. Perhaps a quotation from Bertrand Russell will help to emphasize this point:

" Let us take an instance, in which every sensible man is guided by probability, I mean life insurance. I ascertain the terms on which some company is willing to insure my life, and I have to decide whether insurance on these terms is likely to prove an advantageous bargain, not to insurers in general, but to me. My problem is different from that of the insurance company, and much more difficult. The insurance company is not interested in my individual case: it offers insurance to all members of a certain class, and need only take account of statistical averages. But I may believe that I have special reasons to expect

a long life, or that I am like the Scotsman who died the day after completing his insurance, remarking with his last breath, 'I always was a lucky fellow.' Every circumstance of my health and my way of life is relevant, but some of these may be so uncommon that I can get no reliable help from statistics. . . . The probability at which I finally arrive is thus something quite vague and quite incapable of numerical measurement; but it is upon this vague probability that, as a disciple of Bishop Butler, I have to act."

In the early days of anaesthesia, choice of anaesthetic was a problem that practically resolved itself into the simple issue of which of two agents was more suitable for routine use. Such an issue cries out for statistics, and no doubt the application of modern statistical methods would, for example, have prevented the chloroform committee of 1864 from reaching its unfortunate conclusion. Certainly few anaesthetists today would deny that chloroform has inherent dangers that make it unsuitable for routine use, but the problem is no longer the same. If chloroform is used today, it is not used routinely, but occasionally and for particular reasons, and there are no statistics that can tell us whether this practice is justifiable or not. Even if the giving of chloroform in a particular case results in a smooth and uncomplicated recovery, it is impossible to know the risk to which that case, as distinct from all others, was subjected, and nobody can be in a position to say that it was the "best" anaesthetic.

This realization that choice of anaesthetic is a different kind of problem from what it used to be is fundamental to an understanding of the subject. It is only when we are confronted with a patient to be anaesthetized that we appreciate how little real knowledge we have for our guidance. The question of how much more knowledge it is possible to have in such circumstances leads to philosophical considerations of the nature and extent of knowledge in general, and it is not for me to venture into such realms at the moment. Knowledge of the past, factual knowledge of what happened in a certain case, is not of the same order as knowledge of the future, the ability to predict what will happen in another case, and I think that this inter-relationship is of great importance to us in our dependance on a largely statistical literature. The difficulty of applying evidence from the past to problems in the future has been realized, but perhaps not as fully as it should be. Gillespie lamented the vast number of records he found necessary for the production of a few strictly comparable cases, but, in fact, as long as human beings remain individuals and we believe with Lord Russell that every circumstance of their health and way of life is relevant, there are no strictly comparable cases at all.

How, in the light of these conclusions, can we extend our views on choice of anaesthetic into the future? The chief problem in our immediate future is the profusion of possibilities offered by the ever increasing speed and fruitfulness of physiological and pharmacological research. So many exciting possibilities are arising with regard to new techniques and new drugs that the practising anaesthetist has to face a major ethical problem in deciding how best he may serve the interests of his patients. Is he justified in the clinical trial of unfamiliar methods on the basis of relatively insubstantial reports, and, on the other hand, if they seem to offer real hope to the desperate case, is he justified in withholding them? Now that anaesthesia is not quite such a young subject as it used to be thought, I believe that there is much to be said for settling down to a broadly acceptable and fairly conservative set of standards for routine anaesthetic practice. It is obvious that there is no one drug or technique which is the most suitable for all cases, but a few relatively simple methods will meet practically every contingency, and if these methods are used with intelligence and real skill the need for more exotic expedients almost disappears.

It is not in the best interests of science, or patients, to have innumerable anaesthetists in different places carrying out unco-ordinated clinical trials which are too often made inadequate and misleading by the lack of proper facilities. It occasionally happens already that a valuable new drug waits for some time before receiving a really authoritative trial, while simultaneously, and unknown to each other, half a dozen people are writing papers about the inadequacy of another drug. This kind of reduplication is clearly uneconomical; it causes unnecessary congestion of

the journals, and it represents a wastage of effort which, with so many new possibilities to be investigated, we can ill afford. A great opportunity exists for co-ordinated and well planned research in anaesthesia, rather on the lines of the Medical Research Council's clinical trials which have been carried out concurrently in a number of hospitals, and a powerful central organizing body could be invaluable in this respect. The place for major clinical research and trial is in the teaching centres, where facilities and staff are available—the future of anaesthesia is in the hands of such centres, its present is entrusted to the more peripheral anaesthetist. As the general practitioner of anaesthesia, his prime concern is to treat his patients as they come to him, and to the best of his ability. In this, conventional methods will serve him well; if in addition he should wish to do something more exciting, a central organizing body could supply him with a practicable and useful project for investigation, and thus make him part of a nationwide team working in unison towards a more rapid advancement of anaesthesia than has ever been thought possible.

BOOK REVIEW

A Manual of Anesthesiology. By Herman Schwartz, S. H. Ngai and E. M. Papper. Published by Charles C. Thomas, Springfield, Illinois. Pp. 170; illustrated. Price 32*s*. 6*d*.

There has been need for some time for a primer of anaesthesia, suitably basic in its approach and modern in its outlook. It is doubtful indeed whether a beginner in anaesthesia can ever learn anything of the all important practical techniques of his new specialty from books, and it would seem that in such a primer there would be little place for descriptions of the minutiae of technique which were so characteristic of such volumes fifteen to twenty years ago. Without hesitation one can recommend this admirable little volume for all who are taking up the subject of anaesthesia. Within the 151 pages of text will be found all the general principles of the subject admirably described. The approach to the book is essentially modern in the emphasis it lays on basic principles and functional knowledge. Here you will find no chapters describing individual drugs or particular methods, but you will find sections on "Pulmonary Function", "Neural and Chemical Control of the Heart", "Physics", "Neuromuscular Blockade and its Reversal" and "Principles of Paediatric Anaesthesia". There is a brief (15 pages) survey of the principles of local anaesthesia, and a splendid 4 pages on "Resuscitation"—respiratory and cardiac.

The tables of normal values at the end of the book are admirably in line with this enlightened approach and here will be found not, as so often, weights of cylinders or conversion tables from the apothecaries to metric systems, but average pulse rates, blood pressures and the respiratory characteristics of all ages from the newborn upwards as well as normal values for blood volume, plasma electrolytes, etc. Instead of the size of endotracheal tubes for various ages, are listed the average diameters of the glottis and distances from the lips to all parts of the larynx and trachea.

The use of proprietary names is unfortunate, but as all the drugs mentioned are well known brands of very commonly used preparations this is no great inconvenience. Key references are given at the end of each chapter.

This book is specially and strongly recommended for those beginning their career in anaesthesia.

T. Cecil Gray

Brit. J. Anaesth. (1957), **29**, 284

THE EVOLUTION OF ANAESTHESIA

BY

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(*Continued from Vol.* 28, *page* 594)

THE history of anaesthesia is a large subject; paradoxically, it is also true that it does not exist at all. Anaesthesia is merely a branch of medicine, and its history can only be understood by examining the whole subject. Equally, medicine is a branch of science, while science is but one facet of human activity; it follows, therefore, that the history of anaesthesia can only be interpreted correctly by viewing it in the perspective of other human activities, medical, scientific and social; inventions, discoveries, wars, religious beliefs, and all the manifestations of art and culture.

E. *The Renaissance* (1454–1754).

The great cultural revival which we call the Renaissance cannot be dated accurately. Perhaps its first stirrings can be seen in the writings of Roger Bacon in the middle of the 13th century; certainly the spirit of the Renaissance began to move in literature long before the introduction of printing. The year 1454, however, is a suitable date to choose as the time when the Renaissance began to permeate the lives of all who lived within the bounds of European civilization. The next three hundred years saw the great artistic and scientific advances which overthrew the old Aristotelian and Galenic systems, while the ever-extending areas of commerce and colonization spread the new thought throughout the world, infusing in exchange new ideas, new drugs and new customs into the polity of Western Europe.

As we have seen, the preceding 1250 years had been a period of stagnation: with the budding of the Renaissance, the dead leaves of scholasticism and authority fell away, and man turned from dusty and inaccurate manuscripts to seek the truth in the shining face of nature; no longer did "authority" obscure the truth; observation and experiment, search and research, became of greater and greater importance, and soon yielded undreamed-of treasures.

With all this, the art of printing had much to do. Soon the works of Dante and Boccaccio, medieval in date but modern in spirit, were available for all to read; later the printing presses were working on scientific and medical publications, and books on these subjects appeared at a price far less than that of the manuscript versions. Naturally, the buyers were, at first, the poorer and less literate class, which led to the publication of books especially written for this market. Thus, the first medical book to be printed was the *De Re Medicina* of Celsus, chosen more for the purity of its Latin than for its scientific content, but later medical printed books were of the "Handy Home Doctor" type, written b indigent doctors, like William Bullein, whose *Bulwark of Defence* was written while he was in prison, in the hope of earning a few shillings. Such books were antiquated in spirit and inaccurate in body; they do not reflect the medica science of the time, but that of the earlier period. Naturally, they were despised and criticized by the medical profession who, until the issue of original printed works towards the middle of the 16th century, preferred their manuscripts. However, criticism of unworthy books led to the criticism of all books, printed and manuscript alike, so that the decay of "authority" proceeded with greater rapidity.

Meanwhile the Reformation of Religion was playing its part. The authority of the Pope became weakened, like that of Aristotle and Galen, by observation and by interest in the Scriptures. In all countries, the dominion of the Church became less pervading, and, in some, the Pope's rule was completely cast off. Thus, the way was made clear for scientific investigations which the Church had

previously interdicted. The divorce of Henry VIII from Catherine of Aragon, the final strain which broke the link between England and the Pope, was thus of great importance in the history of Science, for it laid the foundation on which Britain's scientific supremacy was to be built.

The weakening of all authority led to the growth of democracy; the history of the 16th and 17th centuries records rebellion after rebellion which lessened everywhere the power of kings and brought down the feudal system. Thus when, in 1563, Mary Queen of Scots reproached John Knox with interfering in her affairs, saying: "What have ye to do with my marriage, or what are ye within this Commonwealth?", the Reformer replied, "A subject born within the same, Madam, and albeit I neither be Earl, Lord nor Baron within it, yet has God made me (how abject that ever I be in your eyes) a profitable member within the same." As has been said, modern democracy was born in that answer.

By the beginning of the 16th century, the Renaissance in Art was well advanced. Leonardo da Vinci, in the interest of painting, had made many beautiful and accurate anatomical drawings; although these were not then published, they greatly influenced the anatomists to whom he showed them. The discovery of the eliptical arch is another example of the blend of science and art which was to have far-reaching effects.

Paracelsus, whom Osler called "The Luther of Medicine", was the first to throw off publicly the restraint of "authority". When he was appointed Professor of Chemistry and Medicine at Basle in 1526, he began his course of lectures by burning the works of Aristotle, and he further advanced the cause of freedom by delivering his lectures in German, instead of the customary Latin.

The early years of the 16th century are packed with important events, from among which we may select the foundation of the Royal College of Physicians of London (1518), the Incorporation of Barber-Surgeons, later the Royal College of Surgeons of England (1540), the issue of the first book on Physiology since Galen, the *De Naturali Parte Medicinae* of Fernel (1542), the publication of the first modern book on anatomy, the *De Humani Corporis Fabrica* of Vesalius (1543), the posthumous issue of the epoch-making *De Revolutionibus Orbium Coelestium* of Copernicus (1543), and the eponymous naming of syphilis from the poem by Fracastoro (1530).

The overthrow of the classical philosophers in the 16th and 17th centuries created a vacuum which the philosophers of the 17th and 18th centuries strove to fill. In this they were aided by the remarkable achievements in science during the early years of the 17th century. Giordano Bruno, the first to remove the fixed stars from a sphere and to place the boundaries of the universe at an infinite distance, came to the stake in 1600; his influence on scientific thought was great. In the same year Gilbert initiated the study of magnetism by the publication of his *De Magnete*: he introduced the term "electricity" and announced a connexion between electricity and magnetism. In 1601, Kepler, the real founder of modern astronomy, succeeded Tycho Brahe as astronomer to the Emperor Rudolf II. Galileo had made the Aristotelian system shake by his experiments with falling bodies at Pisa in 1591, and he brought it finally to the ground in 1604 by demonstrating that a new star had appeared in Serpentuarius, for the Aristotelian system demanded that the heavens be unchangeable.

Galileo, however, did more than this, for he enunciated the view that science was measurement, thus stimulating, for example, Santorio to invent a clinical thermometer and to carry out his famous weighing experiments by which he proved the existence of "insensible perspiration". A further extension of Galileo's fundamental idea by the mathematical genius of Newton led to the publication of the *Principia* in 1687, under the imprimatur of Samuel Pepys, at that time president of the Royal Society.

The discovery of the circulation of the blood, published to the world in the *De Motu Cordis* of William Harvey in 1628, laid the foundation of modern physiology and medicine, but further developments were delayed by the civil War in England (1642–1649) and by the unrest during the early years of Cromwell's Protectorate. In the latter years of his rule, the Invisible College, later to become the Royal Society, began its work, while the microscopical investigations of Malpighi and Leeuwenhoek, the researches of Boyle in chemistry

and of Boyle and Mayow on air arose from the need for new theories and explanations of the activities of Nature.

Thus, attempts were made to explain the animal body on a mechanical basis, and foremost among workers in this field were Descartes, who first suggested the idea of the nervous reflex, and Borelli, who investigated muscles. Others tried to find answers to the problems of animal economy in the newborn science of chemistry: of these, the most important were Sylvius, who had a clinical laboratory and who propounded a doctrine of acids and alkalis and explained digestion on the basis of fermentation, and de Réaumur, who carried out ingenious experiments on the gastric secretions of birds.

All, however, was not progress: one of the greatest setbacks to scientific advance was the explanation of combustion by postulating the mythical Phlogiston. This theory was propounded by Stahl, a leader of the Vitalist Group, which opposed itself to the Iatrophysicists and Iatrochemists mentioned in the last paragraph.

The 18th century was principally one of consolidation and classification of scientific and medical knowledge, but, within our period, we should mention the work of von Haller, who enunciated the principle of the irritability of muscular and the sensitivity of nervous tissues, and of Boerhaave, who instituted clinical teaching; since the time of Galen, medicine had always been learnt from books and not from observation of the patient. Boerhaave also founded the study of pathology, following such of his patients as died to the postmortem room, and comparing symptoms with lesions. Teaching was improving, and new centres were being opened, foremost of which was the Medical School of the University of Edinburgh, founded by Pitcairne in 1685. Meanwhile, in Britain, the voluntary hospital system was coming into being with the opening of infirmaries, not only in London, but also in the provinces.

Great as were the artistic, cultural and scientific advances of the period under review, the behaviour of "civilized" man left much to be desired. Lunatics were housed and treated in a manner which to us is unbelievably cruel, felons were punished in a most barbarous fashion, debtors were imprisoned in revolting circumstances, and vivisection was practised by men of great renown with a barbaric indifference to the suffering of animals. The pastimes most popular with all classes were brutal: bull-baiting, bear-baiting and cock-fighting. Add to this the almost inconceivable filth and squalor of the towns, with no sanitation, no drainage or cleaning of the streets, the household ordure and garbage rotting in the cellars and thoroughfares to form a stinking slush often more than a foot deep. There was an absence of police, of street lighting, and of a proper water supply; and all, even the rich, swarmed with fleas and lice, and almost never bathed. It is obvious that these were not the conditions in which humanity and human self-respect could flourish. The flower "humanity" was not yet in bud: its fruit was later to be the desire to reduce suffering and, from this, in turn, grew anaesthesia.

The most important incidents which bear directly upon anaesthesia during this period are the discovery of di-ethyl ether (*c.* 1540), the rediscovery of local analgesia by the application of cold (1595 and *c.* 1646), and the experiments on the intravenous administration of drugs and blood undertaken by the Invisible College and its successor, the Royal Society. The idea of anaesthesia, however, was so foreign to the notions of the time that local analgesia by refrigeration was soon forgotten, to be rediscovered a couple of centuries later.

1454. Gutenberg prints from movable type.

1452–1519. Leonardo da Vinci, painter, sculptor, architect and engineer, was one of the most original thinkers the world has ever seen; his art was little influenced by the antique, but was founded upon patient observation. In order to draw the human body more faithfully, he practised anatomy, and his drawings of the heart and other organs, although not published for nearly 300 years, influenced anatomists and others to whom he showed them.

1455. The first battle of St. Albans opens the Wars of the Roses.

1471–1528. Albrecht Dürer, painter and engraver, was much influenced by da Vinci, some of whose anatomical drawings he had seen.

1475–1564. Michael Angelo Buonarroti, sculptor and painter.

1476. Caxton erects the first printing press in England (Westminster). He had printed the first book in English at Bruges in 1475; the first book printed in England, *The Dictes or Sayinges of the Philosphres*, appeared in 1477.

1485. The Battle of Bosworth: the death of Richard III and the accession of Henry VII ended the Wars of the Roses. The period of good government which followed in England provided suitable conditions for the growth of the "New Learning".

1492. Ferdinand and Isabella, uniting the Spanish kingdoms, drive the Moors out of Spain; they help Columbus.

1493. Discovery of North American continent by Columbus.

1495–1553. François Rabelais, priest and physician, author of *Gargantua et Pantagruel*.

1497. Vasco da Gama of Portugal sails round the Cape to India.

1498. Columbus discovers the South American continent. Amerigo Vespucci, a Florentine, later a naturalized Spaniard, explored the coast of Venezuela in 1499. His distorted version of his voyages led to the naming of America after him.

1498. Savonarola tries to reform religion in Florence and is burnt.

1503. The League of Cambrai is made against Venice, then at the height of her power.

1506. St. Peter's at Rome begun by Pope Paul III.

1509–1547. Henry VIII, born 1491.

1513. The Battle of Flodden.

1516. First account of the South American arrow-poison, curare, in the *De Orbe Novo* of Peter Martyr Angherius (1459–1525).

1517. Martin Luther nails his *Theses* on the church door at Wittenberg.

1518. Foundation of the Royal College of Physicians of London. Thomas Linacre (1460–1524), the founder, was a champion of the "New Learning".

1519. Charles V, King of Spain, Archduke of Austria and Duke of Burgundy, becomes Holy Roman Emperor.

1520. The "Field of the Cloth of Gold", a conference in the Pas de Calais between Francis I of France and Henry VIII of England.

1521. South America conquered by the Spaniards; Cortes in Mexico.

1526. Paracelsus (Latin form of his surname, von Hohenheim) (1493–1541) appointed Town Physician and Professor of Chemistry and Medicine at Basle. His arrogance and ill-behaviour, coupled with his lack of respect for Aristotle and Galen, lost him his job in 1528. His writings, which are many, are mystical and obscure. In the *Paradoxa*, published in 1605, he describes the action of oleum vitreoli dulce (di-ethyl ether) on chickens, and states that it "quiets all suffering and relieves all pain". Paracelsus is also credited, on no very good evidence, with the invention of laudanum (tincture of opium). Although not strictly a champion of the "New Learning", his defiance to the authority of the ancients, and his dependence upon experience did much to further the Renaissance in medical thought, and Osler has called him the "Luther of Medicine".

1529. At the Diet of Spires, Luther's followers appear as "Protestants".

1530. Girolamo Fracastoro (1478–1553) publishes his poem, *Syphilis sive Morbus Gallicus*, which gave this name to the disease. Qualified in medicine at Padua, Fracastoro became a man of wide learning. In 1546, he published his *De Contagione et Contagiosis Morbis*, in which he describes a theory of disease based on the existence of living organisms carried in the air or transmitted from person to person. He also contributed to the understanding of astronomy, geology and the nature of fossils.

1532. Henry VIII, unable to obtain the Pope's consent to a divorce, makes himself head of the Church of England and, thereafter, annuls his marriage with Catherine of Aragon.

1534. Ignatius Loyola, the Spaniard, forms the Society of Jesus.

1535. Appearance of Coverdale's Bible, with a title-page designed by Holbein.

1539. Henry VIII orders the dissolution of the monasteries.

c. 1540. Synthesis of di-ethyl ether. The method of synthesis is described by Valerius Cordus, *De Artificiosis Extractionibus Liber*, published in 1561. Cordus (1515–1544) seems to have written this description in about 1540, about the same time as Paracelsus was writing his *Paradoxa* (see 1526). Since Cordus apparently worked with Paracelsus, there is now no means of deciding on the relative responsibility of these two men for this important discovery.

1541. Calvin established as religious dictator at Geneva.

1542. Publication of the *Tratado contra el Mal Serpentino* of Rodrigo de Isla (1462–1542), physician of Lisbon and Barcelona. He states that, at the latter place, in 1493, he treated some of Columbus's sailors for syphilis, and the *Tratado* is the strongest evidence for the American origin of the disease. However, since Columbus did not return from his expedition until 1496, it is doubtful how much reliance is to be placed on de Isla's account.

1542. Jean François Fernel (1497–1558), physician to Henri II of France, and Professor of Medicine at Paris, publishes the *De Naturali Parte Medicinae*. When it was later published as part of his *Medicina* (1554), its name was changed to "Physiologia". It was the first book on physiology since Galen. Fernel also wrote on syphilis, which he believed to be contracted by sexual intercourse, without supernatural interference.

1542. Leonhard Fuchs (1501–1566) publishes his *Commentaries on the History of Plants*. This book was magnificently illustrated and shows considerable advances in the subject of Materia Medica. The plant "fuchsia" is named after him.

1543. Nicholas Koppernik (Copernicus) (1473–1543), mathematician, publishes his great work, *De Revolutionibus Orbium Coelestium*, which showed that the sun was the centre of the planetary universe. The work was completed in 1530, but Copernicus delayed publication until he knew that he was dying, from fear of persecution by the Church.

1543. Publication of the *De Humani Corporis Fabrica*. Andreas Vesalius (i.e., from Wesel) (1514–1564), the founder of modern anatomy, studied medicine at Louvain and Paris. In 1537, he became the first of a long line of distinguished anatomists to occupy the Chair at Padua (e.g. Colombo, Falloppio, Fabrizi) and in 1538 he published his *Tabulae Anatomicae Sex*, a book which was strongly Galenic, describing, for example, the five-lobed liver. However, in 1543 appeared the magnificent *Fabrica*, illustrated by Jakob van Calcar from Vesalius' own dissections and printed by Opporinus of Basle. This book marked a new era: many of its plates have never been equalled either in beauty or accuracy. From this time, anatomy became purely observational, and the way was cleared for the discovery of the circulation of the blood.

1551. Gabriele Falloppio (Fallopius) (1523–1562) becomes Professor of Anatomy at Padua.

1553. Michael Servetus (b. 1509), theologian and physician, went to the stake on account of his religious beliefs, being burnt by the Calvinists, and being equally unpopular with the Pope; his last book, *Christianismi Restitutio*, was burnt with him. This work contains a description of the pulmonary or lesser circulation, which he discovered, but, because only three copies of the book survived, this important discovery was unknown until a much later date.

1556. Agricola (1490–1555), physician, mathematician and mineralogist, called the "father of mineralogy" publishes his *De Re Metallica*.

1558–1603. Queen Elizabeth I.

1559. Realdo Colombo, who succeeded Vesalius at Padua in 1543, publishes his *De Re Anatomica*, in which the pulmonary circulation is described.

1561. Publication of Valerius Cordus's *Annotations on Dioscorides*, in which there are many notable additions to the subject of Materia Medica. The synthesis of ether is also described in a section of this work (see 1540).

1562. Ambroise Paré (1510–1590), surgeon to the French Kings Henri II, Charles IX and Henri III, publishes his *Cinq Livres de Chirurgie*. Although a Huguenot, he was protected by Charles IX during the Massacre of St. Bartholomew (1572). The greatest surgeon of his day, he substituted the ligature for searing with a hot iron as a means of stopping haemorrhage, and also devised ingenious artificial limbs. He disapproved of mandragora, but described local analgesia by compression of nerves.

1562. Publication of William Bullein's *Bulwarke of Defence against all Sickness, Sornes and Woundes that dooe Daily Assaulte Mankinde*. This book has been cited as an authority for the use of mandragora as an anaesthetic, but it is merely a popular and debased version of the typical medieval herbal, issued for the semi-literate and not to be considered as a physician's text.

1563. John Knox (*c.* 1514–1572), in an interview with Mary Queen of Scots (1542–1587), enunciates the principle of modern democracy,. that all members of the State have a right to a say in the conduct of public affairs.

1564–1616. Shakespeare. The plays contain several references to mandragora and to other narcotic preparations, but do not show any real knowledge of the use of such drugs.

1569. Giambattista della Porta (1543–1615), physicist and inventor of the camera obscura, publishes his *Natural Magic*. He describes a preparation of mandragora and other herbs by which means sleep could, he said, be induced, but he did not suggest using the method during surgical operations. He was not a medical man, and there is no evidence that he ever used the preparation, which was an elaboration of the spongia somnifera of the medieval age.

1569. William Chamberlen, a Huguenot, settles in England. He and his descendants kept the family secret of the obstetric forceps, which they had invented, and practised with great success as man-midwives until 1728.

1572. The death of John Knox and the massacre of St. Batholomew.

1577. Frampton's *Joyful Newes Out of the Newe Founde Worlde*, a translation of Nicholas Monardes' *Historia Medicinae* (1574), gives the first account in English of curare, and mentions the coca plant.

1578. Dodoens' *Herbal* mentions the mandrake in the usual way. A mention is also made of the pain-relieving qualities of opium, but it is not suggested for use during surgical operations.

1579. Du Bartas (1544–1590), French poet and soldier, publishes his poem, *La Sepmaine*, which describes the events of the first chapters of Genesis. It was translated into English by Sylvester (1563–1618), whose translation of the account of the birth of Eve has often been quoted. Some have believed that this can be taken as evidence of the use of some sort of anaesthesia for surgical operations at this time, but an examination of the poem shows that it contains nothing more than is explicable by imagination and some knowledge of what the medievalists had written.

1581. The United States of Holland declare themselves independent of Spain.

1582. The Gregorian Calendar supersedes the Julian Calendar in Western Europe. This style of reckoning was not introduced into Scotland until 1600 or into England until 1752, by which time there was a discrepancy of eleven days.

1587. *An Herbal for the Bible* by Lemnius, translated into English by T. Newton, describes the soporific action of mandrake, in connexion with Genesis xxx, 14–17.

1588. The repulse of the Spanish Armada by the English.

1588. De Acosta, after mountaineering in Peru, draws attention to mountain sickness and reports that air above 14,000 feet is not adapted to respiration.

1589. Appearance of the first complete edition of della Porta's *Magiae Naturalis* (vide supra, 1569). In it is a description of the combination of lenses which form a telescope or microscope.

1591. Eufame Macalzean burnt at the stake at Edinburgh. According to some authorities she was executed for attempting to relieve the pains of childbirth, but she was really convicted of witchcraft (vide *Brit. J. Anaesth.*, 1950, **22**, 176).

1595. Sir Walter Raleigh (1552–1618) discovers Guiana. He gives a very highly coloured account of curare poisoning, but the statement that he brought some of the drug to Europe is untrue.

1595. Costaeus, in his *De Ignis Medicinae Praesidiis*, mentions the use of snow or ice for producing analgesia for surgery. This is the first mention of refrigeration anaesthesia since the *Lacnunga* of 1050.

1596–1650. Réné Descartes, philosopher, and originator of the phrase, " Cogito ergo sum ", first gave expression to the idea of the nervous reflex; he believed that all animals, save man, were merely machines. In man, the soul, situated in the pineal body, was able to influence the reflex responses to nervous stimulation.

1600. Giordano Bruno (b. 1548) burnt. His philosophy was strongly anti-Aristotelian, his conception of the universe placed the stars far outside the sphere demanded by Aristotle.

1600. Appearance of the *De Magnete* of William Gilbert (1540–1603), physician to Queen Elizabeth and President of the Royal College of Physicians. He described the magnetic properties of the earth and showed that magnetism and electricity were allied; he introduced the term " electricity ".

c. 1600. Valverdi advocates local analgesia by nerve compression.

1601. Kepler (1571–1630) succeeds Tycho Brahe as Astronomer to the Holy Roman Emperor. His explanation of the laws of planetary motion provided the basis for modern astronomy.

1603. James VI of Scotland becomes James I of England.

1604. Galileo Galilei (1564–1642) shows that a nova in Serpentuarius is a proof of the errors of Aristotle. His support for the Copernican theory in 1632, which he had demonstrated to be correct with the telescope he had constructed in 1624, led to his condemnation by the Inquisition. There is no foundation for the story that his recantation, made in the beautiful gothic Church of Santa Maria Sopra Minerva at Rome, was followed by the traditional phrase, " Eppur si muove ".

1605. Publication of Paracelus' *Opera Medico-Chemica sive Paradoxa* (see 1526 and 1540).

1607–1669. Rembrandt.

1608–1674. Milton.

1614. Appearance of the *De Medicina Statica Aphorismi* of Santorio (1561–1636). A friend of Galileo, he was stimulated by the latter's pronouncement that " science is measurement ". His book contains the well-known picture of himself seated in the balance by which he proved the existence of " insensible perspiration ".

1614. Logarithms described by Napier.

1615. Andreas Libavius mentions the idea of blood transfusion, but there is no reason to believe that he made any experiments.

1618. Beginning of the Thirty Years War, which exhausted Germany and Spain.

1620. Publication of the *Novum Organum* of Francis Bacon, Viscount St. Albans. He showed that knowledge is derived from experience, not from authority, and he described inductive reasoning, which he wished to see applied to science. His death was due to pneumonia from a cold caught while experimenting on stuffing a chicken with snow in the hope of preserving the meat.

1623. Aselli (1581–1626) saw the lacteals when dissecting a dog. His *De Lactibus* (1628) contains the earliest anatomical illustrations in colour.

1624–1674. Thomas Sydenham wrote much, and concentrated on the natural history of diseases: his ideas mark the beginning of a new outlook on disease.

1625. In his *De Thorace*, Hoffman states that the Assyrians produced unconsciousness during the operation of circumcision by compression of the neck. There does not seem to be any foundation for this story.

1628. The Petition of Right.

1628. Appearance of the *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* of William Harvey (1578–1757). Harvey had already expressed his ideas on the circulation of the blood as early as 1616 in his lectures at the Royal College of Physicians, but he waited until his experiments provided complete proof before publication. Harvey had studied under Fabricius ab Aquapendente at Padua. The latter's work on the valves of the veins formed an important link in Harvey's argument. The *De Motu Cordis* is one of the most important books in the history of medicine, for it laid the foundation for modern physiology and medicine.

1637. Opening of the Académie Française in Paris.

1637–1686. Jan Swammerdam, microscopist. His chief work, *Bijbel der Natuur*, was published by Boerhaave in 1737.

1640. Parkinson's *Herbal* advocates mandragora wine as pre-operative medication.

1642. Death of Cardinal Richelieu, who had united and organized France for the crown.

1642. Civil War breaks out in Britain.

1643. Torricelli's barometer.

1646. Severino visited in Naples by Bartholin (see 1661), is using refrigeration with snow or ice as an analgesic for lithotomy.

1648. Van Helmont (1577–1644), who invented the term " gas ", describes " gas sylvestre " (carbon dioxide) in his *Ortus Medicinae*.

1649. Execution of Charles I.

1649. Francis Potter (1594–1678). Aubrey writes: " At the Epiphany, 1649, when I was at his house, he then told me his notion of curing diseases, etc., by Transfusion of Blood out of one man into another, and that the hint came into his head reflecting on Ovid's story of Medea and Jason, and that this was a matter of ten years before that time. About a year after, he and I went to try the experiment, but 'twas on a hen,

and the creature too little and our tools not good. I then sent him a Surgeon's Lancet. Anno 1652, I received a letter from him concerning the subject, which many years since I shewed, and was read and entered in the books of the Royal Society, for Dr. Lower would have arrogated the invention to himself, and now one R. Griffiths, Dr. of Physic, of Richmond, is publishing a book of the transfusion of blood. Mr. Meredith Lloyd tells me that Libavius speaks of the Transfusion of Blood, which I dare swear Mr. F. Potter never saw in his life."

1656. Admiral Blake, shows an English fleet in the Mediterranean.

1656. Christopher Wren (1632–1723), later Savilian Professor of Astronomy at Oxford, experiments with the intravenous administration of drugs to animals.

1656. Giovanni Borelli becomes Professor of Mathematics at Pisa. His *De Motu Animalium* appeared in 1681. He believed that physiology was only a form of physics and, treating the problem of muscular movement as a mathematical problem, achieved considerable results.

1658. François de la Boë (Sylvius) becomes Professor of Medicine at Leyden. He was a leader of the Iatrochemical School.

1658–1695. Purcell.

1660. The Hon. Robert Boyle (1627–1691), son of the Earl of Cork, publishes his *The Spring and Weight of the Air*, in which Boyle's Law is stated.

1660. The Restoration.

1660. Wecker describes a compound of opium, mandrake, hemlock and henbane which will send a man to sleep simply by smelling it: none of these substances is volatile.

1661. Marcello Malpighi (1628–1694) describes the capillaries in the lungs of frogs. Harvey, who had postulated the existence of the capillaries had died four years before the publication of the *De Pulmonibus Observationes Anatomicae*.

1661. Publication of the *De Nivis Usu Medico* of Thomas Bartholinus (1616–1680). A chapter is devoted to refrigeration analgesia, which Bartholin had seen Severino use (see 1646). The Latin text is very corrupt, but it is evident that Osler was wrong in thinking that Severino advocated the use of refrigeration in impending gangrene; in fact, he warned against its use.

1665. Richard Lower (1631–1691) performed the first authenticated transfusion of blood from one animal to another. The experiment is reported at length in the *Journal Book of the Royal Society* (which had been incorporated in 1662). In 1669, he publishes his *Tractatus de Corde*, one of the classics of medical writing.

1666. Appearance of "A Brief Account of Mr. Valentine Greatrakes and divers of the Strange Cases by him lately performed, written by himself in a letter addressed to the Hon. Robert Boyle, to which is annexed the testimonials of several Eminent and Worthy Persons of the Chief Matters of Fact theirin Related." Although some regard Greatrakes as an osteopath rather than a hypnotist, he does seem to have been a precursor of Mesmer. His work was curative rather than anaesthetic; he was known as the "Irish Stroker".

1667. Robert Hooke's (1635–1702) classical experiment, by which a dog was kept alive by inflation of the lungs after the thorax had been opened, and even in the absence of lung movements, when, by puncturing the lungs, air was driven through them. Hooke was Curator to the Royal Society and was a pioneer microscopist. His *Micrographia* (1665) is the first work in which the word "cell" is used in the description of tissues.

1667. First Latin edition of *Clysmatica Nova: sive Ratio qua in venam sectam medicamenta immitti possint* of J. S. Elsholtz. The first German edition had appeared in 1665, but was unillustrated: the 1667 edition has the first illustration ever made of blood transfusion. The book describes the experiments of Lower and Boyle in England, of Major in Kiel, and of Denis in Paris. The latter was the first person to transfuse blood from an animal into a man (1667), an experiment which Lower also performed at about the same time.

1674. John Mayow's *Tractatus Quinque*. This book, an expansion of the *Tractatus Duo* of 1671, deals with respiration, muscular activity and rickets. Mayow showed that a substance occupying about one-fifth of the volume of common air ("spiritus nitro-aereus") was necessary for life and for combustion. He made no attempt to isolate the gas, but he may be said to be the discoverer of oxygen. Mayow's book attracted little attention and was unknown to Priestley and Scheele when they isolated oxygen a century later.

1676. Anton van Leeuwenhoek (1632–1723), petty official of Delft, and a pioneer in microscopy, observes bacteria, but is, of course, ignorant of their nature.

1678. Publication of *Philosophiae Naturalis Principia Mathmatica* of Isaac Newton (1642–1727).

1679. *De Ortu et Occasu Transfusionis Sanguinis* of Mercklin contains the second illustration of blood transfusion. The author considered transfusion dangerous.

1680. Boyle synthesizes ether (Fulton, *Anesthesiology*, 1947, **8**, 465).

1681. The *De Motu Animalium* of Giovanni Alfonso Borelli (1608–1679).

1683. Sobieski the Pole saves Vienna from the Turks.

1685–1754. J. S. Bach.

1685. The Medical School, Edinburgh University, founded by Archibald Pitcairne (1652–1713).

1688–1744. Pope.

1689. William of Orange, King of England, is the chief opponent to a powerful France under Louis XIV. The Bill of Rights.

1690. Dr. John Locke (1632–1704) issues his *Essay on Human Understanding*.

1693. *The Armamentarium Chirurgicum* of Scultetus contains a somewhat fancifui illustration of blood transfusion.

1694–1778. Voltaire (François Marie Arouet).
1697–1763. William Smellie, a great pioneer in obstetrics, and teacher of William Hunter.
1704. The capture of Gibraltar makes England a Mediterranean power.
1704. Newton synthesizes ether (Fulton, *Anesthesiology*, 1947, **8**, 465).
1705. Purmann's textbook of surgery illustrates (very badly) and describes blood transfusion.
1707. In his *Physicians Pulse-Watch*, Sir John Floyer describes a watch which ran for 60 seconds. The construction of a watch with a seconds hand was impracticable at this date. Although Santorio had sought to measure pulse-rate by means of a pendulum, Floyer's work really begins the counting of the pulse.
1707. Act of Union of England and Scotland.
1709. Hermann Boerhaave becomes Professor of Medicine at Leyden.
1709. Peter the Great of Russia defeats Charles XII of Sweden at Pultowa.
1709–1784. Dr. Samuel Johnson.
1718. The *De Anaesthesia* of J. B. Quistorp uses the word "anaesthesia" almost in its modern sense, and speaks learnedly of its derivation. He does not, however, mention surgical anaesthesia.
1720. Alexander Monro primus (1697–1767), a pupil of Boerhaave, becomes professor of anatomy at Edinburgh. He, his son and his grandson held the chair until 1846.
1720. The South Sea Bubble.
1721–1742. Walpole is Prime Minister.
1724. Guy's Hospital opened a week after the death of its founder, Thomas Guy, publisher and merchant.
1730. W. G. Frobenius publishes *An Account of a Spiritus Vini Aethereus*, in the Philosophical Transactions of the Royal Society. This is an account of the "oleum vitreoli dulce" which has subsequently been known as ether.
1731. Georg Ernst Stahl (1660–1734) propounds the Phlogiston Theory of Cumbustion in his *Experimenta et Observationes Chemicae*.
1733. Meisser describes (*Skizzen*, 1782) how "Augustus, king of Poland and elector of Saxony (Augustus II, otherwise Frederick Augustus I) (1670–1733) suffered from a wound in his foot which threatened to mortify. . . . During sleep, induced by a certain potion surreptitiously administered, his favourite surgeon cut off the decaying parts." The whole incident (transferred by Ellis, *Ancient Anodynes*, 1946, to Stanislaus Poniatowski) is apocryphal, except that Augustus died as a result of his wound.
1736. Albrecht von Haller (1708–1777), one of the great geniuses, becomes Professor of Medicine at Göttingen.
1743(?) *An Account of the Extraordinary Medicinal Fluid called Aether*, by Matthew Turner. He describes the history and manufacture of ether, and adds directions for its use in headache: "In stubborn cases it will likewise be serviceable to snuff a little of the aether up the nostrils." An heroic measure which hardly entitles him to a place as an originator of pain-relief by the inhalation of ether vapour.
1745. De la Condamine brings a specimen of curare to Europe and demonstrates its action on hens.
1748. Pomet, in *A Complete History of Drugs*, states that mandragora "was formerly esteemed to have a strong narcotic quality, . . . but it is now never used."
1752. Réné de Réaumur (1658–1757) describes the action of gastric digestion in his *Sur la Digestion des Oiseaux*.
1752. The Gregorian Calendar is introduced in England, September 2 being succeeded by September 14 (see 1582).
1753. Publication of the *De Somno; de Medicamento Somniferis et de Natura Hominis in Somno*, of L. C. Fabri, an early contribution to sleep-producing drugs, and of *A Treatise on Opium*, by George Young.
1753. Publication of *A Treatise of the Scurvy*, by James Lind (1716–1794), in which the use of lemon juice is shown to be of value in preventing the disease.
1753. Publication of the *Species Plantorum* of Karl von Linné (Linnaeus, 1717–1783), when the use of specific names on a binomial system is first employed.

(To be continued)

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assess the potency of the analgesic. It would appear, however, that Proladone is a long acting analgesic without the potency of the morphine derivatives. The routine now adopted is to give a single dose of Proladone 10 mg postoperatively. As a rule this proves adequate, but where the pain impulses are incompletely covered pethidine in 25 mg doses is given until a satisfactory sedation is produced.

To revert to the normal pre-operative sedatives with morphia, papaveretum or pethidine as suggested by Belam would appear, from my limited trial, unnecessary, and to deny the patient the outstanding features of Proladone, namely a long acting analgesic which does not cause respiratory depression or vomiting.

IAN MCCULLY,
Royal Infirmary, Bradford

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND

Provisional Programme, Jubilee Meeting, 1957

at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

Wednesday evening, December 4

Cocktail Party to welcome overseas visitors attending the meeting. (By invitation only.)

Thursday, December 5

Morning: Scientific Session. Short Papers.

LUNCH

Afternoon: Annual General Meeting. Faculty of Anaesthetists, Royal College of Surgeons. Frederic Hewitt Lecture.

TEA

Evening: Annual Dinner in the Great Hall at the Royal College of Surgeons. (Tickets £2 12*s.* 6*d.* each, inclusive of wines.)

Friday, December 6

Morning: Scientific Session. Short Papers.

LUNCH

Afternoon: Scientific Session. Short Papers.

TEA

Evening: Meeting of the Section of Anaesthetics of the Royal Society of Medicine. (By kind permission of the President and Council of the Section of Anaesthetics, this meeting will take place at the Royal College of Surgeons.)

Evening: Cocktail Party given by the Faculty of Anaesthetists, Royal College of Surgeons. (By invitation only.) Buffet-Dance at Londonderry House, Park Lane, London, W.1. (Tickets £3 3*s.* 0*d.* each, including buffet supper.)

Saturday, December 7

Morning: Symposium on anaesthetic apparatus, considered especially from the point of view of performance.

LUNCH

Afternoon: Panel discussion on anaesthetic apparatus.

A number of firms will be exhibiting in Room I and the Museum Hall throughout the Meeting, and there will also be a small Scientific Exhibition.

Registration fee: £2 0*s.* 0*d.* (This includes morning coffees, lunches and teas.)

The detailed programme will be circulated in the early autumn. Particulars available from: The Secretary, Association of Anaesthetists of Great Britain and Ireland, 45 Lincoln's Inn Fields, London, W.C.2.

CORRESPONDENCE

CLINICAL TRIAL OF NEW ANALGESIC

(Belam, O. H., *Brit. J. Anaesth.*, **29**, 190)

Sir,—The use of morphine and its derivatives, and to a lesser extent pethidine, has side effects which have long been the bane of the anaesthetist. Notable among these are postoperative nausea, vomiting and respiratory depression. With a view to preventing, or at least limiting these side effects, it was decided to try dihydro-hydroxy codeinone pectinate (Proladone) for pre-operative medication. The drug was given routinely to all patients over the age of ten years and for all forms of general surgery, ranging from simple superficial procedures to major abdominal resections. The dose of Proladone (10 mg) was combined with atropine 0.6 mg and given intramuscularly 1 hour before operation. It was found very early on that the drug as it was given was inadequate for pre-operative sedation. The patients arrived in the anaesthetic rooms awake, alert and apprehensive. Attempting to tranquilize the patients 9(1 methyl 3 piperidyl methyl) phenothiazine (Pacatal) was added to the premedicant in 50 mg dosage. This addition failed to produce the desired effect.

For the past five months the atropine has been replaced by hyoscine 0.6 mg. The combination has proved very satisfactory, the patients arriving in the anaesthetic rooms in very much the condition associated with papaveratum scopolamine. In the elderly where hyoscine is contra-indicated a reversion has been made to morphine and atropine and in the very young where hypnosis is more important than analgesia the drug has been discontinued. In the remainder, however, between the ages of 10 and 65 years premedication with Proladone 10 mg with hyoscine 0.6 mg one hour before operation, relaxant, N_2O/O_2 sequence with intramuscular Pacatal 50 mg has proved essentially satisfactory. The absence of postoperative nausea and vomiting has been gratifying to both the patients and the anaesthetist who has to face them the following morning.

It is extremely difficult in clinical practice to

[*Continued on page 291*

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VOLUME XXIX No. 6 *Published monthly* JUNE 1957

Annual subscription (post free): Inland £3 15*s.*: *Overseas* £4 4*s.*: *U.S. and South Americas* $12.00

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